Local Aggressive Treatment in Oligometastatic NSCLC

Subjects: Surgery

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In oligometastatic NSCLC, the treatment of all tumor sites should be technically feasible with tolerable toxicity. It was thus proposed that oligometastatic NSCLC should include five or fewer metastases in three or fewer organs. Notably, the primary tumor and an involvement of mediastinal lymph nodes are excluded as a metastatic site, while pulmonary or pleural metastases are counted as a metastatic site. Patients with diffuse serosal metastases (meningeal, pericardial, pleural, or peritoneal) or bone marrow involvement are as well excluded from the definition of oligometastatic NSCLC, for they cannot be treated with radical intent. In general, most (oligo) metastases of NSCLC are found in the brain (35.5%), followed by the contralateral lung (33.6%), the adrenal glands (10%), bones (8.5%), and the liver (2.4%). One-fourth of all patients with metastatic non-small cell lung cancer presents with a limited number of metastases and relatively low systemic tumor burden. This oligometastatic state with limited systemic tumor burden may be associated with remarkably improved overall and progression-free survival if both primary tumor and metastases are treated radically combined with systemic therapy. This local aggressive therapy (LAT) requires a multidisciplinary approach including medical oncologists, radiation therapists, and thoracic surgeons.

non-small cell lung cancer | oligometastatic | lung cancer surgery | local aggressive therapy

1. Surgical Treatment for Oligometastatic Non-Small Cell Lung Cancer

For LAT of oligometastatic NSCLC, surgical resection has traditionally been the main treatment modality, with more than 50% of all patients receiving surgical treatment in early systematic reviews [1]. Berzenji et al. recently summarized the two most common treatment approaches: The first approach (**Figure 1**B) includes an initial aggressive resection of the primary tumor, followed by the resection or SBRT of metastatic lesions. Systemic treatment (preferably targeted treatment in NSCLC with targetable oncogenic drivers or immunotherapy in NSCLC without targetable oncogenic drivers but PD-L1 expression >1%) is subsequently used for the control of micrometastatic disease [2]. A second option for addressing oligometastatic NSCLC is a neoadjuvant systemic treatment as described above, followed by a PET-CT-based re-staging and subsequent resection (**Figure 1**A). In non-progressive or oligoprogressive disease, the resection of the primary tumor and an aggressive treatment of distant metastases by either resection or SBRT follow thereafter in a so-called “salvage” surgery concept [2][3]. Upfront surgery offers the advantage of performing surgery without delay and without the risk of a decline in the

functional status after an induction treatment. However, no down-staging is possible and extensive open resections such as pneumonectomies or sleeve resections are often required [4].

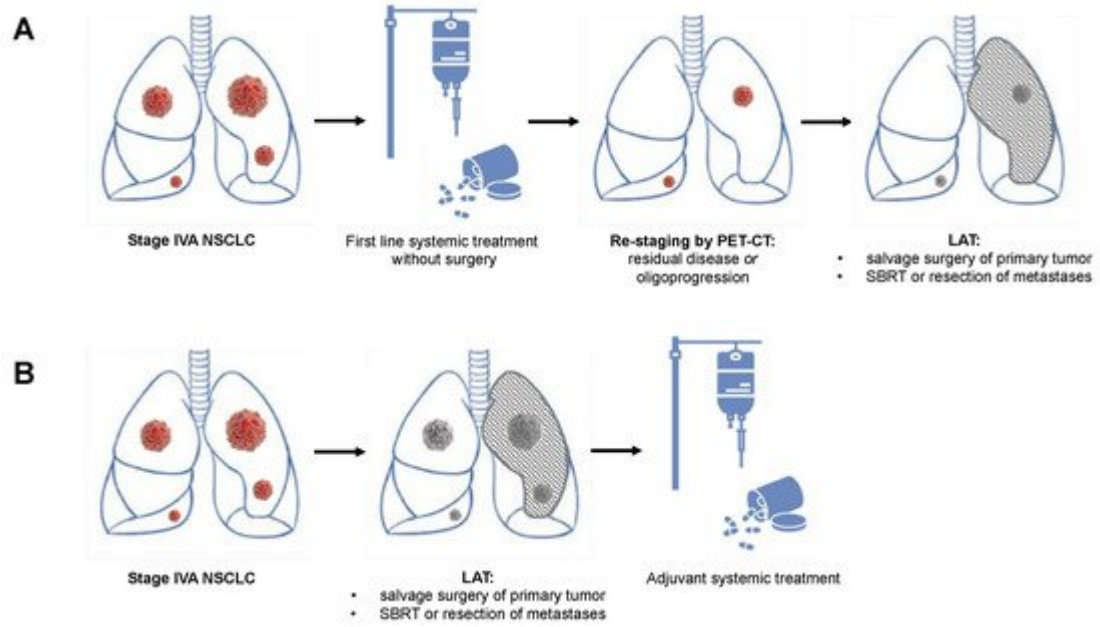

Figure 1. Schematic presentation of the two potential multimodality approaches including local aggressive treatment (LAT) of oligometastatic non-small cell lung cancer with contralateral pulmonary metastases. (**A**) Scheme involving systemic induction treatment, followed by re-staging and LAT with salvage surgery in case of residual disease or oligoprogression. (**B**) Primary LAT with surgical resection or radiation therapy of the primary tumor and all metastatic lesions, followed by adjuvant systemic treatment. LAT: local aggressive therapy.

In contrast, neoadjuvant treatment is administered with the intent to eradicate nodal and micrometastatic disease and achieve a reduction in tumor volume and burden, which subsequently enables a complete resection of the remaining tumor (**Figure 2**) [4]. In addition, neoadjuvant systemic treatment is more likely to provide access for both surgical and systemic treatment modalities to a larger number of patients, while a substantial number of patients may not be able to complete adjuvant treatment if an extensive surgery was performed upfront [4]. Finally, neoadjuvant systemic treatment allows assessing the treatment response and treatment-induced changes in tumor biology on histopathological and molecular levels [4]. This information may provide additional guidance to decide on the further treatment steps. What needs to be considered, however, is that surgery after neoadjuvant treatment may be more challenging than upfront surgery. Especially after combination regimens with chemotherapy and immunotherapy, increased vascular fragility and interstitial exudation, compacted or calcified hilar or mediastinal lymph node stations, and fibrotic changes render surgery in these patients more difficult [5]. However, despite these challenges, even extensive resections in locally advanced stages and after induction with immunotherapy can be safely performed with 90-day mortality rates between 0% and 3% [6][7][8]. The ideal timing of LAT within a multimodality treatment approach is, thus, highly debated and several ongoing clinical trials are currently evaluating different schemes of LAT in combination with targeted therapy, immunotherapy, and/or chemotherapy (**Table 1**).

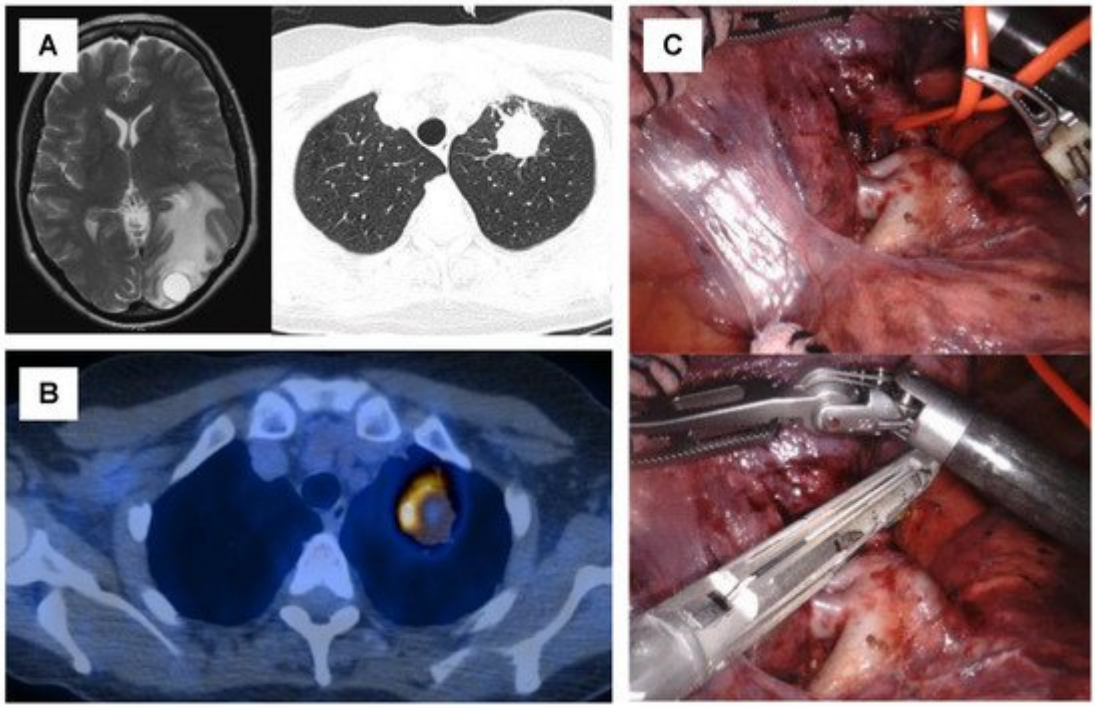

Figure 2. Case of a 57-year-old patient with oligometastatic lung squamous cell carcinoma with a single synchronous brain metastasis and no sign of mediastinal nodal involvement (**A**). The patient underwent surgical resection of the brain metastasis, followed by six cycles of platin-based chemotherapy. Re-staging by PET-CT showed a stable disease of the primary tumor and no signs of additional metastases (**B**). Subsequently, a robotic-assisted thoracoscopic (RATS) upper left lobectomy was performed to complete the local aggressive therapy (LAT) (**C**).

Table 1. Ongoing clinical trials for local aggressive therapy including surgery in oligometastatic non-small cell lung cancer. LAT: local aggressive treatment. OPD: oligoprogressive disease. OS: overall survival. PFS: progression-free survival. SBRT: stereotactic body radiation therapy.

Study Abbreviation	ClinicalTrails.gov Identifier	Phase	Setting	Type of Systemic Treatment	Type of LAT	Timing of LAT	n	No. of Metastases	Primary End Points	Planned Completion
14-18 CHESS	NCT03965468	II	Synchronous oligometastatic NSCLC	Durvalumab, Carboplatin, Paclitaxel	Primary: Surgery or radical radiotherapyMetastases: SBRT	Neoadjuvant systemic treatment	47	Max. 3	PFS	12/2021
OMEGA	NCT03827577	III	Oligometastatic NSCLC	Standard medical therapy	Surgery, Radiotherapy, RFA	Neoadjuvant systemic treatment or primary LAT	195	Max. 3	OS	09/2022
n/a	NCT02759835	II	EGFR-mutated OPD NSCLC	Osimertinib	Surgery, SBRT, radiofrequency ablation	LAT after oligoprogression	37	n/a	PFS	09/2022

Study Abbreviation	ClinicalTrails.gov Identifier	Phase	Setting	Type of Systemic Treatment	Type of LAT	Timing of LAT	n	No. of Metastases	Primary End Points	Planned Completion
						under first-lineOsimertinib				
n/a	NCT02316002	II	Oligometastatic NSCLC	Adjuvant Pembrolizumab	Completed first-line treatment (surgery, SBRT, radiotherapy, chemotherapy)	Any first-line treatment followed by adjuvant pembrolizumab	51	n/a	PFS	09/2022
LONESTAR	NCT03391869	III	Stage IV NSCLC (incl. OMD subgroup)	Nivolumab and ipilimumab	Surgery, radiotherapy	Combined neoadjuvant and adjuvant immunotherapy	270	n/a	OS	12/2022
NORTHSTAR	NCT03410043	II	EGFR-mutatedStage IIIB or IV NSCLC (incl. OMD subgroup) [9][10][11]	Osimertinib [9][10][11]	Surgery, radiotherapy	Combined neoadjuvant and adjuvant Osimertinib	143	[9][12][13][14][15] n/a	PFS	01/2023
LAT-FLOSI	NCT04216121	IIb	EGFR-mutated OPD NSCLC	Osimertinib	Surgery, SBRT	LAT after oligoprogression under first-lineOsimertinib	39	Max. 3	PFS	08/2023

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and PFS of 75.1% and 22.2% were found [16]. A recent retrospective study by Jones et al. additionally supports the concept of a neoadjuvant induction in stage oligometastatic NSCLC by showing that patients who received neoadjuvant therapy had a significantly improved 5-year OS of 40% when compared to the cohort of patients who had received primary surgery (20% 5-year OS) [17]. However, when compared to neoadjuvant chemotherapy followed by local radiotherapy, primary surgery followed by adjuvant chemotherapy still appears to offer an increased median OS (48 months versus 18 months) [18].

The use of pleurectomy and decortication for malignant pleural effusion or disseminated pleural metastases without extrathoracic disease has only been investigated in small sample sizes [19]. Currently, there is no evidence from larger studies and clinical trials to provide a recommendation for LAT in patients with malignant pleural effusion or disseminated pleural metastases [19].

2. Radiation Therapy for Oligometastatic Non-Small Cell Lung Cancer

Data on the use of radiation therapy for oligometastatic NSCLC are currently limited, but the majority of the contemporary data supports the use of consolidative SBRT in patients with stable disease or partial response to first-line systemic treatment or in patients with oligoprogression during systemic therapy [20]. Especially in the era of immunotherapy, the combination of SBRT and immune checkpoint inhibitors has been shown to modulate the tumor microenvironment and increase the trigger for a systemic anti-cancer response [20][21]. Most current studies and guidelines recommend an upfront systemic therapy, followed by LAT using SBRT with or without surgery. The American Radium Society currently recommends a cutoff of three metastatic sites or fewer to receive consolidative SBRT [20]. In patients with four to five metastatic lesions, SBRT should be considered on a case-by-case basis. However, the current consensus guidelines are based on smaller phase II trials, while results from larger phase III trials are pending [20]. An enrollment in an ongoing phase 3 trial is, therefore, encouraged when SBRT is planned in patients with oligometastatic NSCLC [20].

3. Patient Selection Criteria for Local Aggressive Therapy

Since the evidence of LAT for oligometastatic NSCLC is increasing, the identification and characterization of the patient cohort that will benefit from a LAT strategy has been essential and was highly debated ever since. However, the clinical heterogeneity and broad spectrum of therapeutic approaches make it difficult to identify clear clinical prognostic factors. Here, we discuss a group of prognostic factors that are either associated with the clinical outcome after LAT or are considered to be fundamental for an aggressive treatment of the primary tumor.

3.1. Site of the Primary Tumor

In many metastatic NSCLC, the primary tumor is as well locally advanced and may present with an infiltration into the central airways, large vessels, the chest wall, or neurovascular structures, as in pancoast tumors. For a successful LAT, disease control not only concerns the metastatic sites, but also the primary tumor. Current evidence shows that a complete resection of the primary tumor (R0-resection) is critical for the OS and PFS of patients undergoing LAT. R1/R2 resections are associated with a significantly worse OS and PFS than R0 resections in a retrospective analysis of 53 patient [22]. Therefore, extended resections such as sleeve-resections or intrapericardial pneumonectomies should be performed in selected cases if necessary to achieve tumor-free resection margins. Surgical treatment of locally advanced NSCLC may require an intraoperative stand-by or support of extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass and may need an experienced postoperative intensive care. Surgery of oligometastatic NSCLC should, therefore, be reserved to expert centers with sufficient case volume. In cases with an unresectable primary tumor, either due to the local extent of the disease or due to a reduced functional capacity, SBRT offers an alternative approach that has been shown to provide favorable local control rates [23][24][25][26]. While in the past, SBRT has mostly been used in situations where surgery was not feasible, recent studies have proven the safety, feasibility, and efficacy of SBRT in oligometastatic NSCLC [23][24][25][26]. However, no clinical trials comparing a surgical approach to SBRT in this setting have been published to date [2].

3.2. Site of Metastases

According to the EORTC consensus statement, oligometastatic disease is defined as the stage in which long-term disease control can be gained by LAT. Serosal metastases or bone marrow metastases are, thus, excluded from this definition as they cannot be controlled by local therapy. For solitary metastases in other organs, the size and location as well as the accessibility for surgical resection are essentially influencing the indication for surgical treatment. The decision whether the primary tumor or a metastasis is suitable for surgical resection should always be made in a multidisciplinary tumor board, but it lastly lies in the hands of the surgeon to decide on functional and anatomical feasibility.

The brain is the most common site for distant metastasis in NSCLC and aggressive treatment of cerebral oligometastases including a combination of surgery and radiotherapy is associated with improved OS, improved functional status, and decreased chances for cerebral recurrence [27][28]. Patients with unresectable single brain

metastases should be treated with stereotactic radiosurgery or definitive radiotherapy [28]. Similarly, relatively good prognoses have been reported in adrenal oligometastases after radical adrenalectomy [28]. In a study by Raz et al., a median survival of 19 months and 5-year survival of 34% was seen in patients with oligometastatic NSCLC and isolated adrenal metastases undergoing adrenalectomy, whereas patients who were treated without adrenalectomy showed a median survival of 6 months and a 5-year survival of 0%. In particular, patients with ipsilateral adrenal metastases had a significantly improved 5-year survival when compared to contralateral adrenal metastases [29].

3.3. Mediastinal Lymph Node Involvement

Mediastinal lymph node involvement has been determined as a predictor for poor prognosis in patients who undergo LAT for oligometastatic NSCLC [30][28][31][32]. Many authors, therefore, conclude that patients with N0 disease are the ideal candidates for LAT, with a 5-year survival up to 21% in patients with synchronous brain metastases and 51% in patients with isolated adrenal metastases [33][28][29][31][32][34]. The role of mediastinal lymph node involvement is further highlighted in the population of oligometastatic NSCLC with extracranial and extra-adrenal metastases. The 5-year survival rate in this population was 64% in patients with N0 status, but 0% in patients with N2 status [32]. Patients with pathologically confirmed N2 disease should, therefore, not be candidates for LAT. In this perspective, we also recommend that suspected lymph node metastases should always be confirmed by bronchoscopy and EBUS or mediastinoscopy in patients with oligometastatic NSCLC. This is especially important in patients who have undergone an induction treatment with immunotherapy and may show pseudoprogression upon restaging by PET-CT [35].

3.4. Synchronous and Metachronous Metastases

While synchronous metastases are defined as a manifestation of distant metastases within 6 months of the primary tumor's diagnosis, metachronous metastases occur more than 6 months after the initial diagnosis [36]. In a large meta-analysis by Ashworth et al., prognostic factors after curative, local, consolidative treatment of oligometastatic NSCLC were evaluated. Metachronous metastasis was a significant predictor for an improved OS (multivariable hazard ratio 3.02) in the cohort and was, therefore, included into a risk classification scheme based on recursive partitioning analysis. The authors describe a low-risk group with metachronous metastases (5-year OS 47.8%), an intermediate-risk group with synchronous metastases and no mediastinal lymph node involvement (5-year OS 36.2%), and a high-risk group presenting with synchronous metastases and N1 or N2 disease (5-year OS 13.8%) [33][36]. Similar findings were reported in a systematic analysis of 114 patients with adrenal metastases of NSCLC. In this cohort, median OS was significantly shorter in synchronous metastases when compared to metachronous metastases (12 months vs. 31 months) [37].

3.5. Performance Status

In a multicenter analysis of 124 patients with oligometastatic NSCLC who underwent resection of the primary tumor in Switzerland, a 5-year survival of 83% and a low perioperative morbidity and mortality were found in a subgroup of younger patients (<60 years) with a negative nodal status [30]. These findings fall in line with other studies where patients with a good performance status, aged <65 years, and with solitary metastases survived longer [38][39].

Accordingly, patients who had experienced a weight loss >10% had a significantly decreased median OS of 6 months versus 28 months [22]. The decision for LAT should be made in a multidisciplinary tumor board and functional parameters such as respiratory reserve and a cardiac risk score should, therefore, always be taken into consideration [30]. The improved survival of patients with a good performance status also suggests that this group of patients is more likely to be selected for an aggressive treatment protocol, extensive surgical resection, or a second-line treatment after relapse [30].

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