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10th International Workshop on Surgical Exploration of the
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OLIGOMETASTATIC NON-SMALL CELL LUNG CANCER (NSCLC). EVIDENCE FOR SURGICAL TREATMENT

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Oligometastatic non-small cell lung cancer (NSCLC) represents a wide spectrum of diseases and encompasses a very heterogeneous patient population. A distinction should be made between synchronous and metachronous oligometastatic disease, oligopersistence and oligoprogression (1). A wide range of definitions is found in literature. The European Organisation for Research and Treatment of Cancer (EORTC) established a multidisciplinary task force to obtain a more uniform definition (2). A maximum of 5 metastatic lesions and 3 organs is proposed. All organs are allowed except for bone marrow and diffuse serosal metastases. In the 9th edition of the TNM classification of NSCLC, category M1c (multiple distant metastases) is subdivided into M1c1 when multiple metastases are present in a single organ system, and M1c2 when multiple metastases are present in multiple organ systems (3). Bone and muscle are considered to be one organ system. However, no precise cut-off point could be found regarding the number of metastases in relation to survival, and hence no definition of oligometastases is provided.

Current data suggests that local ablative therapy (LAT) of oligometastatic lesions with surgery or stereotactic body radiation therapy (RT) may result in improved overall survival and progression-free survival (PFS) rates. However, the precise role of surgical resection has not been clearly established yet, but it is clear that surgery should be part of a multimodality treatment protocol.

The indications for surgical treatment depend on a number of metastasis-related factors such as the number, size, and location of metastases, and on patient-specific factors such as age, performance status, comorbidities, and prognosis. Both brain and adrenal oligometastases have shown to have relatively good prognoses after radical treatment with surgery, with 5-year overall survival (OS) rates of 20% and 20-30%, respectively. In general, patients with synchronous metastases and positive lymph nodes have the poorest prognosis.

When considering LAT in patients with oligometastatic disease, complete imaging work-up is required by PET-CT scanning and preferentially, also MRI of the brain instead of a CT scan.

Which therapeutic algorithms may be proposed? Evidence from large randomized, phase III trials is not available but treatment outcomes of salvage surgery in oligometastatic NSCLC were studied in a phase II, multi-center, randomized controlled trial (4-5). Patients with histological confirmation of stage IV NSCLC and 3 or fewer metastatic lesions after first-line systemic therapy were included. After inclusion, patients were randomly assigned to either local consolidative treatment (LCT consisting of RT or surgical resection of all lesions) with or without subsequent maintenance treatment, or to maintenance treatment alone. The study was terminated early

after randomization of 49 patients (25 patients in the LCT group and 24 patients in the maintenance group) when an interim analysis showed that LCT extended PFS compared to maintenance therapy alone. Of the 25 patients in the LCT group, 6 patients (24%) underwent a combination of surgery and RT, and one patient (4%) received surgery to all sites. No grade 3 or 4 toxicities were reported. The median PFS in the LCT was 11.9 months, versus 3.9 months in the maintenance group. Time to appearance of new lesions was 11.9 months in the LCT group compared to 5.7 months in the maintenance group. In a follow-up study, also OS was significantly different between both groups with a p-value of .017 (5). The authors concluded that, in patients with 3 or fewer NSCLC metastases, aggressive local therapy with or without maintenance therapy resulted in improved PFS and OS rates compared to maintenance treatment alone.

How shall we proceed in daily practice? Current recommended selection criteria for surgical resection of oligometastatic NSCLC include (6):

- multidisciplinary tumor (MDT) board discussion
- a maximum of 5 metastatic sites
- preoperative biopsy strongly preferred
- mandatory PET-CT and brain MRI within 30 days of procedure
- mandatory pathological mediastinal nodal assessment by EBUS or mediastinoscopy
- all metastatic sites must be treatable by surgery (complete resection), RT, ablation or a combined modality approach
- in case of doubt whether a lesion is a metastasis or new primary cancer expert pathologic review and genotyping are recommended
- for patients with > 1 extracranial metastasis, starting with a course of systemic therapy is favored.

The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines of 2019 made following statements (7):

- in case of 1-3 synchronous metastases long-term disease-free survival (DFS) may be obtained after systemic therapy and LCT, but inclusion in clinical trials is preferred
- in patients with limited metachronous metastases long-term DFS may be obtained after radical local treatment but inclusion in clinical trials is preferred
- solitary lesions in the contralateral lung are mostly synchronous second primary tumors and should be treated with curative-intent therapy

Key References

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