Oligometastatic disease has been described more than 25 years ago by Hellman and Weichselbaum as a distinct cancer state, characterized by a limited metastatic capacity, where definitive local treatment in addition to standard of care systemic therapy may offer a curative potential (1,2). At the time of the seminal editorial, the evidence supporting the oligometastatic hypothesis was based on retrospective observational studies, where better than expected long-term overall survival was observed after metastasectomy (3). Today, several prospective and randomized phase II trials support the integration of definitive local treatment into a multimodality treatment strategy for oligometastatic lung cancer (4-6), oligometastatic prostate cancer (7-9), oligometastatic colorectal cancer (10) or even in disease-agnostic oligometastatic cancer patients (11). Only one randomized trial did not observe a benefit of the interventional arm of definitive local metastases-directed therapy: this single negative trial enrolled patients with oligometastatic breast cancer, and has been reported only in abstract form (12). The consistent trial outcomes and the clinically relevant survival improvements resulted in a widespread adoption of this treatment strategy (13).

Despite this rapid progress in clinical research, many uncertainties remain to be addressed to further improve outcome of oligometastatic cancer patients. Highest level of evidence in the form of randomized phase III trials is still lacking to support metastases-directed local treatment (14). However, despite these trials are underway, the large heterogeneity of (oligo-) metastatic cancer patients with respect to their underlying cancer biology and the associated rapidly evolving personalized systematic treatment strategies will not allow to test the local intervention in all clinical settings; randomized trials are need as proof-of-principle and large population based registries such as the ESTRO/EORTC OligoCare project might complement these randomized trials, and contribute to an improved understanding of oligometastatic disease and patient selection. The definition of oligometastases is today based on counting imaging-based metastases, and most clinical trials used a maximum of n=3 or n=5 metastases as trial inclusion criteria (15), which is observed in many unselected cancer patients (16). More sensitive imaging will therefore have immediate impact on patient selection, which might result in both over- and undertreatment (17). Recent studies have further indicated that the volume of metastatic disease burden might be an independent prognostic factor in addition to the number of metastases (18).

However, identical disease representation on imaging might be associated with very different clinical situations: e.g., disease recurrence of a solitary metastasis several years after curative treatment of localized cancer vs. progression of one solitary metastasis after previous complete response to systematic therapy for widespread metastatic cancer. This need to consider the longitudinal clinical course of disease and the response to systemic therapy was recognized by the ESTRO & EORTC oligometastatic disease classification system: this classification system differentiates between de-novo, repeat and induced oligometastatic disease and further subclassifies between oligo-recurrent, oligo-progressive and oligo-persistent disease depending on the response to systemic therapy (19). The classification system aims to standardize the nomenclature of different oligometastatic states, and improve inter-trial comparability. Additionally, first studies successfully validated the prognostic value of this classification system (20).

However, it is unlikely that clinical and imaging-based characteristics will be sufficient to guide the optimal multimodality treatment strategy in oligometastatic cancer patients. Biological characterization of oligometastatic disease has been evaluated in several studies: microRNA expression analyses (21), molecular subtyping (22) or mutational analyses (23) have been proposed but remain to be validated. Recent insights into the clonal evolution might further contribute to identification of patients with a low risk of widespread systemic disease (24). Liquid biopsy is another promising tool to better characterize (oligo-)metastatic cancer patients, especially if performed longitudinally over the course of treatment (25,26).

Another complexity in oligometastatic cancer patients is the need to treat several metastases irrespective of their size and anatomical location and potentially the primary tumor with definitive local intent while simultaneously address the high risk of occult microscopic disease with most effective systemic therapy. From a local treatment perspective, surgery has been the traditional standard, which was replaced by stereotactic radiotherapy as the most frequently applied local treatment modality in recent prospective and retrospective studies (27). The favorable therapeutic ratio of stereotactic radiotherapy combined with its non-invasive nature and possibility to continue systemic therapy uninterrupted are arguments in favor of radiotherapy, while surgery is preferred especially when large tissue sampling is needed. The optimal systemic treatment strategy is frequently adapted from stage IV standards of care. However, several studies proposed alterative treatment strategies and clinical endpoints such as definitive local therapy to defer the initiation of systemic therapy in indolent disease such as oligometastatic prostate cancer (7,8) or renal cell cancer (28). Optimal sequencing of local and systemic therapy is

another field with many uncertainties (29).

Overall, it is obvious that oligometastastic cancer represents a multidimensional challenge requiring a multidisciplinary approach in diagnosis and treatment. This book will contribute to bring different perspectives and approaches together and contribute to a better understanding of oligometastatic disease.

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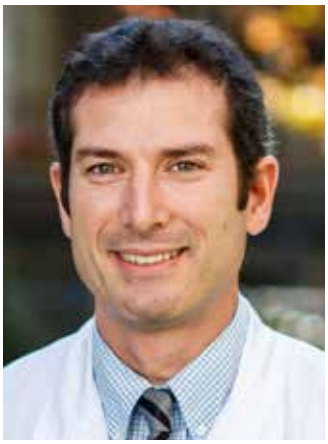

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