



Expanding the knowledge of oligometastatic disease – but uncertainties remain significant

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Most patients with lung cancer present with advanced disease at the time of diagnosis, when local curative therapy is no longer a treatment option. Among patients with early lung cancer, who are initially treated in curative intent, 6–7% will go on to develop oligometastases, where the metastatic spread is limited in number and site (1). This oligometastatic condition has been suggested to represent a biologically less aggressive tumor state, lying somewhere between complete lack of metastases and diffuse metastatic spread. It has been described as an evolutionarily intermediate metastatic state, with more of a tendency to remain stable over time (2). Local ablative therapy aims to render patients' disease free by interrupting the cascade of metastatic seeding from existing sites, and although molecular genetic studies may eventually help provide a better understanding of the oligometastatic state (3), the mechanisms by which local ablative therapy works, remain speculative (4). Because most patients with stage IV non-small cell lung cancer (NSCLC) will eventually experience disease progression it is important to identify those with oligometastatic disease (confirmed by clinical follow-up) who may benefit from local ablative therapy, in addition to inductive systemic therapy.

In “Lung Cancer”, Arrieta and colleagues present the results of a contemporary single-arm phase II study on radical consolidative treatment in patients with synchronous, oligometastatic NSCLC (5). The article addresses several key points, including the significance of

PET-CT in evaluating treatment response and determining patient selection, as well as the benefit of local ablative therapy for patients with synchronous oligometastatic disease.

The study includes 43 NSCLC patients, initially treated in curative intent and presenting with up to five distant metastases. All patients received systemic treatment (either 4 cycles of first-line chemotherapy or in cases of EGFR or ALK rearrangement a targeted agent) and were then evaluated on the basis of PET-CT for response. The 37 patients who displayed either stable metastatic disease or partial response then received radical consolidative therapy (surgery in 38.7%, radiation therapy in 80.6%, chemoradiation in 19.4%, and radiofrequency ablation in 6.5% of the detected metastases), 51.4% of patients showed complete response following radical consolidative therapy, and 48.6% showed partial response. Those with complete response also had significantly better overall and progression free survival. Twelve patients had oligo- or local progression during follow-up but had better overall survival than the 10 patients who developed polymetastatic disease. Arrieta and colleagues concluded that radical consolidative therapy is a viable treatment option in patients with synchronous oligometastatic NSCLC and that PET-CT is a valuable diagnostic tool, both in determining which patients may benefit from radical consolidative therapy and in predicting long-term survival. Since synchronous oligometastatic disease seems to display a more aggressive

oncologic behavior than metachronous disease, particular care must be taken in determining which subset of patients with oligometastases will truly benefit from local consolidative treatment (6).

In many studies, the disease-free interval between the initial curative treatment of the primary cancer and the onset of mono-metastases did not influence overall survival (7-9). Other authors however (10,11), report significantly lower survival rates for patients with early postoperative oligo-recurrences. This has led to the recommendation for inductive systemic therapy followed by local consolidative therapy for patients with three or fewer synchronous oligometastases (12).

The precise definition of how many metastases comprise an oligometastatic state, however, is still debated. In this study by Arrieta and colleagues, patients with up to five metastases were candidates for local ablative therapy (5). In a study by Salama *et al.* (13), patients with between 1 and 3 metastases at enrollment demonstrated better outcomes (60.3%, 2-year overall survival) than those with 4 or 5 metastases (21.9%, 2-year overall survival), and those with 4 or 5 metastases often went on to experience widespread metastatic progression when the follow-up was long enough. It is not surprising that patients with a lower metastatic burden at the outset might have a better outcome after local ablative therapy (13), but ultimately the maximum number of lesions that can justify the risks of radical consolidative therapy remains unknown, meaning that future studies are warranted.

In the study by Arrieta *et al.* (5), 40.5% of oligometastases were contralateral lung metastases, which are known to be biologically less aggressive than extrathoracic synchronous oligometastases (6). In clinical practice, however, similarities in morphology and even histology make it difficult to differentiate between second primary lung cancers and pulmonary metastases. For this reason, solitary-metastases within the lung should be evaluated using immunohistochemical and molecular techniques whenever possible and should be discussed within a multidisciplinary team.

Interestingly, Arrieta and colleagues found that patients with mediastinal lymph node involvement did not have significantly worse overall survival than those without (5). The study may have been underpowered, but even still, mediastinal lymph node metastases at the time of lung cancer diagnosis should not automatically exclude patients from consideration for local ablative treatment. Ashworth and coworkers' meta-analysis of 757 NSCLC patients with between 1 and 5 synchronous or metachronous metastases

offers some interesting perspectives on this question (11). Here, all primary lung cancers and metastatic lesions were treated in curative intent with surgical metastasectomy, stereotactic radiotherapy/radiosurgery, or radical external-beam radiotherapy. Patients were grouped as being at high, intermediate, or low risk for recurrence, based on time of metastatic onset, chronicity (metachronous versus synchronous), and lymph node status at the time of primary lung cancer diagnosis. Here, the authors found that 5-year overall survival ranged between 13.8% for patients with synchronous onset and hilar/mediastinal lymph node metastases, and 47.8% for patients with metachronous metastases and no malignant lymph involvement.

A major limitation of most studies using non-surgical techniques such as radiotherapy, of course, lies in the lack of histological verification of the metastatic lesions. This is particularly significant in patients with solitary metastatic lesions, where lesions that are not actually metastases may be mistaken as such. Additionally, the published evidence, which is largely based on small, retrospective case-series, is limited by a certain selection bias. Additionally, while there is mostly a long-time frame necessary for patient recruiting in retrospective case series, there are many changes in treatment regimen that may have occurred and affect the study results.

More recently, however, two phase 2 randomized trials in patients with oligometastatic NSCLC were started and then stopped after interim analyses found a dramatic improvement in progression free survival after local ablative interventions. In the multi-institutional study by Gomez and coworkers (14), 49 patients with three or fewer lesions, who had all received first-line systemic therapy, were randomized to receive either radical consolidative therapy or maintenance chemotherapy alone. Of the patients selected for local consolidative therapy, most were treated with radiation and less than 25% with surgery. Patients with local consolidative therapy had a median progression free survival of 11.9 months, compared to 3.9 months in those receiving systemic therapy alone. Another (single-institution) study by Iyengar *et al.* (15) enrolled 29 patients with a maximum of 5 metastases, who had demonstrated either a response or stable disease after induction chemotherapy. Fourteen patients were randomized to receive stereotactic ablative radiotherapy as local consolidative therapy, and here too, progression free survival was nearly three times longer in patients receiving local ablation therapy, compared to those receiving maintenance chemotherapy alone (9.7 *vs.* 3.5 months). A most recently published multicenter trial

of 99 patients, by Palma and coworkers (16), analyzed outcomes after stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with a variety of advanced stage cancers (SABR-COMET). Although most patients in the intervention group had breast or prostate cancer, 12 patients with lung cancer and up to 5 metastatic lesions were included. Those treated with stereotactic ablative therapy demonstrated a median progression free survival of 12 months, compared to 6 months in the control group. This came, however, at the cost of radiation-induced toxicity and a treatment related mortality of 4.5% (16).

In summary, the evidence for defined prognostic parameters remains limited. For this reason, treatment of oligometastatic disease should still be decided on a case-by-case basis in a multidisciplinary tumor board. Although there is no general consensus on the precise definition of oligometastatic disease, local treatment of oligometastatic lesions has become common practice (17). The bulk of evidence on the topic comes from retrospective, non-randomized investigations, and the few prospective series available are relatively small phase II studies. Currently ongoing, however, are phase III investigations like the STOP-NSCLC trial for oligo-progressive lung cancer (NCT02756793), the SARON-trial (NCT 02417662), and the NRG LU002 trial; as well as two investigations of targeted cancer therapies: HALT (for oligo-progressive disease) and the NORTHSTAR trial, which seek to identify patients most likely to benefit from metastasis directed therapies. Most studies of local consolidative therapy apply radiotherapy. Surgery, however, offers the often-overlooked advantages of providing better local control, more accurate staging, and also tissue acquisition for molecular analyses—which are ultimately the basis of targeted therapies. Whether immunotherapies—perhaps in combination with radiation to induce an abscopal effect—may further benefit patients with oligometastatic disease remains to be fully investigated (18).

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Footnote

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