



## Current treatment landscape for oligometastatic non-small cell lung cancer

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## Abstract

The management of patients with advanced non-small cell lung carcinoma (NSCLC) has undergone major changes in recent years. On the one hand, improved sensitivity of diagnostic tests, both radiological and endoscopic, has altered the way patients are staged. On the other hand, the arrival of new drugs with antitumoral activity, such as targeted therapies or immunotherapy, has changed the prognosis of patients, improving disease control and prolonging survival. Finally, the development of radiotherapy and surgical and interventional radiology techniques means that radical ablative treatments can be performed on metastases in any location in the body. All of these advances have impacted the treatment of patients with advanced lung cancer, especially in a subgroup of these patients in which all of these treatment modalities converge. This poses a challenge for physicians who must decide upon the best treatment strategy for each patient, without solid evidence for one optimal mode of treatment in this patient population. The aim of this article is to review, from a practical and multidisciplinary perspective, published evidence on the management of oligometastatic NSCLC patients. We evaluate the different alternatives for radical ablative treatments, the role of primary tumor resection or radiation, the impact of systemic treatments, and the therapeutic sequence. In short, the present document aims to provide clinicians with a practical guide for the treatment of oligometastatic patients in routine clinical practice.

**Key Words:** Oligometastatic; Non-small cell lung carcinoma; Non-small cell lung cancer; Oligometastasis

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**Core Tip:** The treatment of oligometastatic non-small cell lung cancer patients remains controversial. The lack of solid evidence for the best therapeutic strategy and the multiple options currently available for both systemic and local treatments make this particular population of patients a challenge for clinicians. Improvement of surgical and radiotherapy techniques and the appearance of different ablative methods, such as radiofrequency or cryoablation, have made it possible to radically treat metastases in any location. In addition, recent prospective studies suggest that combining these ablative therapies with systemic treatments improve patient outcomes. We discuss the current status of the management of oligometastatic patients.

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## INTRODUCTION

Up to two-thirds of patients diagnosed with non-small cell lung cancer (NSCLC) present with advanced disease on diagnosis, or develop incurable metastases during the course of the disease[1]. Despite the heterogeneity of this group of patients, their treatment is largely systemic. In recent years, new systemic treatments have appeared, such as tyrosine kinase inhibitors (TKIs) with molecular targets or immunotherapy (ICI), which have significantly improved the efficacy of these systemic treatments, leading to prolonged survival in candidates for targeted therapies or immunotherapy. Moreover, the prognosis is very different for patients with a low metastatic volume. This is reflected in the 8<sup>th</sup> tumor-node-metastasis (TNM) classification, which distinguishes between patients with a single extra-thoracic metastasis, M1b stage IVA, and patients with multiple lesions in one or multiple organs, M1c stage IVB [2]. Patients with a low metastatic burden, also referred to as oligometastatic, can benefit from local treatment of the primary tumor and metastatic sites. The term oligometastatic, coined by Hellman and Wichselbaum in 1995[3,4], refers to an intermediate situation between potentially curable local neoplastic disease and incurable widespread metastatic cancer. In the case of NSCLC, oligometastatic patients constitute 26% to 50% of patients with advanced disease, depending on whether the cutoff is taken at  $\leq 3$  or  $\leq 5$  metastatic locations[5,6]. Precisely, the main challenge for an optimal approach to oligometastatic disease has been the lack of consensus in its definition. Recently, the European Consensus defined oligometastatic state as a maximum of five metastases from up to three different sites[7], although this definition is not unanimously accepted by the scientific community, and some

prospective studies developed in this context define oligometastatic stage as a maximum of three metastases.

Initially, surgery was the only radical treatment that could be offered to these patients. Now, however, thanks to technological advancements, they can receive ablative irradiation doses by stereotactic body radiotherapy (SBRT) at cranial and extracranial levels, which is both safe and well-tolerated. When local treatment of metastases is combined with systemic treatment, 5-year survival rates between 8.3% and 86% can be achieved[8]. Three randomized studies in oligometastatic patients have shown that this radical local treatment of metastatic locations increases progression-free survival (PFS) and even benefits overall survival (OS)[9-11]. However, it is still unclear which patients can benefit from this strategy. Although there is a lack of consensus about the definition of oligometastases, for some patients with oligoprogression, local treatment of these sites can increase PFS without exhausting new lines of systemic chemotherapy (CT).

In this review, we propose to explore the most controversial aspects of patients with oligometastatic NSCLC, examining in greater depth aspects such as: the definition of this condition, the selection of patients, and the combination of systemic and local treatments.

## THE DEFINITION OF OLIGOMETASTATIC DISEASE

Oligometastatic lung cancer refers to a group of patients with stage IV NSCLC, who present with limited metastatic disease in terms of the number of lesions and organs affected. The incidence of oligometastatic NSCLC has been estimated at between 27% and 55%, depending on the series published [12]. The most frequent oligometastatic location is the brain (36%), followed by the contralateral lung (34%), suprarenal gland (13%), bones (9%), and liver (2%)[13]. Oligometastatic disease, more accurately referred to as an oligometastatic state, can have a more indolent biology than widespread metastases, or at the least, microscopic disease that can be eradicated with systemic therapy. This limited metastatic phenotype could benefit from local aggressive therapy known as consolidation therapy. In fact, an ongoing study is examining different epigenetic markers such as microRNAs[14], to determine their ability to distinguish between the oligometastatic state and widespread metastases. This distinction together with the determination of different prognostic factors are crucial to select patients in whom radical treatment of the primary tumor and of the oligometastases could improve PFS and OS[9].

Currently, the concept of limited metastatic disease is not clearly defined and there is some discrepancy among authors. A European multidisciplinary group recently agreed to accept the definition of oligometastatic disease as the presence of up to five metastases in three different organs[7]. However, this is not universally accepted and additional studies are required to standardize the concept of oligometastases. Within the oligometastatic state, different patterns of presentation of the disease and its response to treatment can be clearly distinguished. The term synchronous or “*de novo*” oligometastatic disease refers to the initial simultaneous diagnosis of both the primary lung tumor and a limited number of metastases. This presentation pattern appears to have a worse prognosis than metachronic oligometastatic disease or oligorecurrence, in which the patient develops distance metastases after having received radical treatment with curative intent of the primary lung tumor, with an apparent local control of the disease[12,15]. In both patterns, the oligometastatic phenotype seems to reflect the biology of the underlying tumor rather than being related to any specific previous therapy. Another two patterns correspond to patients with initially widespread metastases who receive systemic treatment and achieve a partial response, consisting of the stable persistence of a small number of oligometastases (oligopersistent disease or “induced oligometastasis”) with possible later progression (oligoprogression). These scenarios are more common among patients treated with targeted therapies who present acquired resistance to treatment.

## ALTERNATIVES TO ABLATIVE TREATMENT OF METASTASES

The main local treatments in oligometastatic disease correspond to surgical resection, radiotherapy treatment, and ablative radiofrequency techniques[16]. Although there are no prospective studies that compare the efficacy of these treatments, the main characteristics and published evidence for each of these therapeutic alternatives are described below.

## SURGERY

Traditionally, surgery has always been the elective approach in oligometastatic patients[17]. Surgical indication depends on several factors relating to the metastases (size, number, and locations), and also on patient-related factors (age, performance status, comorbidities, and prognosis). Over the past decade, the rate of metastectomies among NSCLC patients has increased and these mainly correspond to

interventions on lung, brain, and adrenal gland metastases. Moreover, mortality has declined with the development of less invasive advanced surgical techniques[18]. Most evidence for the benefits of surgery can be found in studies on patients with brain metastases. Patchell *et al*[19] randomized 48 patients with a single brain metastasis (77% of whom were diagnosed with NSCLC) to whole brain radiotherapy (WBRT) or surgical resection of the metastasis followed by WBRT. The results demonstrated an increased local control and OS in the group treated surgically. Few studies on the surgical resection of extracranial metastases have been published and most of these are retrospective and highly heterogeneous regarding time of onset of the metastases and their location[20-22].

## RADIOTHERAPY

Thanks to technological advances in recent years, large doses of radiation can be delivered with high precision to several sites. Brain metastases are treated with stereotactic radiosurgery and extracerebral lesions with SBRT, or stereotactic ablative radiotherapy (SABR). One of the advantages of these treatments is that they require fewer sessions, each of a short duration. They are also safe, produce minimum toxicity, and do not require long interruptions in systemic chemotherapy.

Most studies are retrospective, but some prospective randomized phase II studies focusing on the efficacy and safety of these techniques have produced promising results[8-10,23-28] (Table 1). Results are pending, over the next few years, for several ongoing phase 3 studies[29,30] (Table 2).

## RADIOFREQUENCY ABLATION

The radiofrequency ablation (RFA) technique consists of applying high frequency microwaves by means of a catheter inserted inside the tumor to destroy the tissue with heat. RFA has been used for both primary lung tumors and pulmonary metastases. Simon *et al*[31] treated 153 patients with primary or medically-inoperable metastatic NSCLC with RFA. For stage I NSCLC, they reported OS at 1, 2, and 5 years of 78%, 57%, and 27%, respectively. Tumoral control was 83%, 64%, and 47% at 1, 2, and 5 years for tumors of 3 cm or less, and for tumors larger than 3 cm, was 45%, 25%, and 25%, respectively. The incidence of pneumothorax was 28.4% (52 of 183 sessions) and 9.8% (18 cases) required placement of a drain. More recently, Picchi *et al*[32] reported a retrospective series of 174 patients with lung cancer treated with 264 CT-guided ablation sessions. In patients with primary lung lesions, the OS rates were 66.73% at 1 year, 23.13% at 3 years, and 16.19% at 5 years. In patients affected by metastatic lung lesions, the OS rates were 85.11%, 48.86%, and 43.33%, respectively, at 1, 3, and 5 years[32]. Although evidence is scarce, these experiences support CT-guided RFA in patients with primary and metastatic lung cancer as an alternative therapy in non-surgical candidates.

## CRYOABLATION

This technique destroys the tissues by extreme cold and freezing. Cryoablation is currently used routinely to treat lung cancers with specific clinical indications. Bronchoscopic cryoablation is an accepted, standard-of-care for the safe and effective treatment of obstructing endobronchial tumors in the central airways[33-36]. Cryoablation has also been used as a treatment option for unresectable primary and secondary peripheral lung tumors[37,38].

Recently, high rates of tumoral control and promising survival outcomes have been reported in a series of patients with metastatic lung cancer lesions treated with this technique[39], although more research is required to verify these findings.

## THE ROLE OF SURGERY AND RADIOTHERAPY IN PRIMARY TUMORS

Local therapies in primary tumors should conform with the principles governing a good control of the pulmonary neoplastic disease and, in this context, the concept of oligometastatic disease has become a different entity. The most important prognostic factor is the stage of spread according to the TNM classification, but in recent years histological subtype, lymphovascular spread, and genetic and molecular alterations have gained in importance[40].

In the treatment of primary tumors per se, the type of patients is an important prognostic factor that can affect survival[41]. The lymph nodes should be examined thoroughly to rule out pathological mediastinal or hilar involvement. This is an important prognostic factor as it could indicate lymphatic and hematogenic spread, thus limiting the options of intrathoracic control and would also increase the risk of spread of the metastatic disease[12].

**Table 1 Main studies on stereotactic body radiotherapy for the treatment of oligometastatic non-small cell lung carcinoma**

Ref.	Year	Patients (n)	Site of oligo-metastasis	N	Dose (Gy/fraction)	Systemic therapy	Median follow-up (mo)	Median PFS (mo)	Median OS (mo)
Retrospective studies									
Inoue <i>et al</i> [27]	2010	41 <sup>1</sup>	Brain, lung, adrenal	< 5	48/8 (adrenal)35-60/4-8 (lung)	NA	20	3-yr PFS 20%	24
Hasselle <i>et al</i> [28]	2012	25	Multiple	< 5	24-70/3-20	Various	21	4.2 (all); 12 (1 met)	23 (1 met)
De Rose <i>et al</i> [26]	2016	60	Lung	< 5	48-60/3-8	Chemo	28	32.2 (actuarial)	32.1 (actuarial)
Single arm prospective trials									
Salama <i>et al</i> [23]	2012	61 <sup>1</sup>	Multiple	< 5	24-48/3	Chemo	20.9	2-yr PFS 22%	2-yr OS 56.7%
De Ruyscher <i>et al</i> [20]	2012	40	Multiple	< 5	54/3 <sup>2</sup>	Chemo	27.7	12.1	13.5
Collen <i>et al</i> [29]	2014	26	Multiple	< 5	50/10	Chemo	16.4	11.2	23
Randomized phase II trials									
Gomez <i>et al</i> [25]	2016	49	Multiple	< 3	NR	Chemo	12.4	14.2 <i>vs</i> 4.4	41.2 <i>vs</i> 17
Iyengar <i>et al</i> [10]	2018	29	Multiple	< 5	21-37.5/1-5	Chemo	9.6	9.7 <i>vs</i> 3.5	Not reached <i>vs</i> 17
Palma <i>et al</i> [11]	2019	99	Multiple	< 5	35-60/3-8	Chemo	25	12 <i>vs</i> 6	41 <i>vs</i> 28

<sup>1</sup>Diverse primary histology including non-small cell lung carcinoma.

<sup>2</sup>Only 1 patient received stereotactic body radiotherapy.

Chemo: Chemotherapy; N: Number of oligometastatic lesions per patient; NA: Not applicable; NR: Not reported; OS: Overall survival; PFS: Progression-free survival.

On the other hand, the type of local therapy chosen should guarantee complete local control. Surgery is the most frequent local treatment in published studies[41]. Moreover, for a therapeutic approach to oligometastatic disease, complete resection (R0) must be performed[42]. In the case of surgery, the patient's clinical condition must be good enough to ensure not only that the tumor can be resected, but that the patient can withstand an operation. In other words, that the patient's overall cardiologic and respiratory functional status are sufficient to permit surgical intervention.

The role of radiotherapy and its modalities depend upon the stage of the primary tumor. In the case of external curative radiotherapy (EBRT), this is defined by delivery of a biologically effective dose (BED) higher than or equal to 60Gy<sub>10</sub>. In the case of SBRT with intention-to-treat, a BED higher than or equal to 100 Gy<sub>10</sub> is required[43]. In the initial stages, SBRT is indicated when surgical intervention is not possible, or when the patient refuses surgery[43]. EBRT is only used in non-operable patients, who do not fulfil criteria for SBRT. In stage III, if the lesion is potentially resectable, the combination of radiotherapy and chemotherapy plays a dominant role within multimodal treatments, either pre or post-operatively[44].

In this stage, if the tumor is unresectable, the elective treatment is radiotherapy delivered concurrently with chemotherapy. Sequential administration is possible if the size of the tumor makes it difficult to deliver sufficient radiation. Radiation therapy can also be delivered alone if chemotherapy is contraindicated[45].

## SYSTEMIC TREATMENT IN THE OLIGOMETASTATIC PATIENT

In the management of oligometastatic NSCLC patients, local treatments of surgery or radiotherapy have been used to reduce tumoral burden and prolong OS and PFS. For years, the evidence supporting this strategy was mainly provided by retrospective studies in which encouraging results were observed in patients treated with local ablative therapies compared to those receiving systemic therapy alone[7]. The recent publication of some randomized prospective studies has provided valuable information to help

**Table 2 Ongoing studies on stereotactic body radiotherapy in oligometastatic non-small cell lung carcinoma**

Title	Patients	Study design	Estimated completion
Stereotactic Ablative Radiotherapy for Oligometastatic Non-Small Cell Lung Cancer. A Randomised Phase III Trial Institution: University College London Clinical Trials.gov identifier: NCT02417662	340	Phase 3 multicenter: chemotherapy alone or chemotherapy + radical radiotherapy (conventional RT and SABR) Primary histology: all NSCLC 1-3 oligometastatic lesions Primary outcome measure: OS	August 2022
Maintenance Systemic Therapy Versus Local Consolidative Therapy (LCT) Plus Maintenance Systemic Therapy for Limited Metastatic Non-Small Cell Lung Cancer (NSCLC): A Randomized Phase II/III Trial (NRG LU-002) Institution: NRG Oncology Clinical Trials.gov identifier: NCT03137771	400	Phase 2/3 multicenter: maintenance chemotherapy or SBRT + maintenance chemotherapy Primary histology: all NSCLC 1-3 oligometastatic lesions Primary outcome measure: PFS	August 2022
Randomized Phase III Trial of Local Consolidation Therapy after Nivolumab and Ipilimumab for Immunotherapy-naïve Patients with Metastatic NSCLC (LONESTAR)-Strategic Alliance: BMS Institution: M.D. Anderson Cancer Center Clinical Trials.gov identifier: NCT03391869	360	Phase 3 multicenter; systemic treatment only with nivolumab and ipilimumab, or induction nivolumab and ipilimumab followed by local consolidative therapy with surgery and/or radiotherapy Primary histology: all NSCLC 1 oligometastatic lesions Primary outcome: OS	December 2022
A Randomised Trial of Conventional Care Versus Radioablation (Stereotactic Body Radiotherapy) for Extracranial Oligometastases Institution: Royal Marsden NHS Foundation Trust Clinical Trials.gov identifier: NCT02759783	245	Phase 2/3 multicenter: standard of care + SBRT Primary histology: breast, prostate or NSCLC 1-3 oligometastatic lesions Primary outcome measure: PFS	October 2024
A Randomized Phase III Trial of Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of 4-10 Oligometastatic Tumors (SABR-COMET 10) Institution: Lawson Health Research Institute Clinical Trials.gov identifier: NCT03721341	159	Phase 3 multicenter: stereotactic ablative radiotherapy, plus standard of care treatment; chemotherapy, immunotherapy, hormones, or observation given at the discretion of the treating oncologist Various histology including NSCLC 4-10 oligometastatic lesions Primary outcome: OS	January 2029
Randomized Phase II Trial of Osimertinib With or Without Local Consolidation Therapy (LCT) for Patients With EGFR-Mutant Metastatic NSCLC (NORTHSTAR) Institution: M.D. Anderson Cancer Center Clinical Trials.gov identifier: NCT03410043	143	Phase 2 multicenter: osimertinib followed by local consolidative therapy with surgery and/or radiotherapy or maintenance osimertinib alone Primary histology: NSCLC > 1 oligometastatic lesion Primary outcome: PFS	January 2023
A Multicenter Single Arm Phase II Trial Assessing the Efficacy of Immunotherapy, Chemotherapy and Stereotactic Radiotherapy to Metastases Followed by Definitive Surgery or Radiotherapy to the Primary Tumor, in Patients With Synchronous Oligometastatic Non-small Cell Lung Cancer Institution: European Thoracic Oncology Platform Clinical Trials.gov identifier: NCT03965468	47	Phase 2 multicenter: durvalumab, carboplatin/paclitaxel chemotherapy, followed by SBRT to all oligometastases. Restaging at 3 mo definitive local treatment with surgical resection of primary tumor or RT 60-66 Gy to the primary tumor if not disease progression 1-3 oligometastatic lesions Primary outcome: PFS	December 2023

OS: Overall survival; PFS: Progression-free survival; RT: Radiotherapy; SABR: Stereotactic ablation radiotherapy; SBRT: Stereotactic body radiotherapy.

treatment decisions in this setting.

The SABR-COMET study is a phase II prospective clinical trial in which 99 patients with different types of oligometastatic tumor (a maximum of 5 metastatic sites) were randomized to receive SBRT and standard systemic treatment, or systemic treatment alone<sup>[11]</sup>. Ablative treatment with SBRT significantly increased OS [41 mo *vs* 28 mo, hazard ratio (HR): 0.57, 95% confidence interval (CI): 0.30-1.10]. Only 18 patients in this cohort had a primary lung tumor, thus making it difficult to extrapolate

the results for application in this patient group. In the SBRT-treated group, a higher proportion of patients had breast and prostate cancer. The less aggressive history of these entities could also affect outcomes. However, a post-hoc analysis which excluded patients with breast and prostate cancer still found a significant benefit for patients receiving ablative radical treatment, with a survival rate at 5 years of 33% compared with 16% in patients receiving the standard treatment.

More recently, the findings of several phase II clinical trials in patients with lung cancer have been published. Iyengar *et al*[10] published the results of a phase II clinical trial in 29 patients with oligometastatic advanced NSCLC who had completed induction chemotherapy with disease response or stabilization. Patients were randomized to receive maintenance chemotherapy *vs* SBRT on all tumoral sites followed by maintenance chemotherapy[10]. A significant increase in PFS was observed in the patient group receiving the radical treatment (9.7 mo *vs* 3.5 mo;  $P = 0.01$ ), with excellent local control of irradiated sites and no rise in toxicity. Similarly, Gomez *et al*[9] published the results of a phase II trial in which 49 patients with advanced lung cancer, with three or fewer metastases at diagnosis, had been treated with induction therapy and were randomized to receive local radical treatment and maintenance with standard systemic therapy *vs* systemic therapy exclusively. They found significant differences in both PFS (14.2 mo *vs* 4.4 mo;  $P = 0.022$ ), and in OS (41.2 mo *vs* 17 mo;  $P = 0.017$ ) in favor of the combined treatment[9].

More recently, the annual conference of the American Society of Clinical Oncology reported the results of the SINDAS study. This phase III randomized clinical trial explored the role of stereotactic radiotherapy combined with first or second generation tyrosine kinase inhibitors of epidermal growth factor receptor (EGFR) (tyrosine kinase inhibitor [TKI]-EGFR) *vs* TKI-EGFR alone in first-line treatment of patients with EGFR-mutant advanced oligometastatic lung adenocarcinoma, with five or fewer metastatic lesions[46]. A total of 133 patients were included (65 in the TKI arm) and 68 in the TKI-SBRT arm, finding a significant difference in favor of the experimental arm for both PFS [20.2 mo *vs* 12.5 mo, HR: 0.6188 (95%CI: 0.3949-0.9697);  $P < 0.001$ ] and OS [25.5 mo *vs* 17.4 mo, HR: 0.6824 (95%CI: 0.4654-1.001);  $P < 0.001$ ], with no increase in toxicity[46].

## CONCLUSION

Oligometastatic disease (OMD) is a unique condition characterized by a limited number of metastases and an indolent evolution. Because of the different prognosis of this condition, the TNM classification considers stage IV with a single metastatic site as a different category, called stage IV1b[2]. However, the World Health Organization classification is much more heterogeneous and includes patients with a greater number of metastases (up to 5 for some authors). Because of this difference, in an attempt to reach a consensus, the European Organization for Research and Treatment of Cancer established the most accepted definition to be the presence of five metastases and three affected organs after staging with computed tomography/positron emission tomography (CT/PET) and brain magnetic resonance imaging[14]. Noteworthy, the main points to consider in OMD are that all lesions (primary lesions and metastases) can be managed with an intention-to-treat approach and that the goal of treatment must be curative.

Growing interest in OMD has arisen from three main developments. First, an improvement in diagnostic techniques, mainly with the use of CT/PET in lung cancer staging, has resulted in an increasing number of patients being diagnosed with fewer metastases. The prognosis of this group is also better[21]. Moreover, technological advances in the field of radiotherapeutic oncology mean that high doses of radiation can be applied to specific sites. This non-surgical approach is preferred by patients with OMD as they can avoid the morbidity and mortality derived from surgical intervention. Over the past few years, the number of studies into the use of SBRT in OMD has been increasing. These have not only focused on brain metastases, but also on metastases of liver, lung, bone, and multiple organs, reporting local control rates of 70%-90% and a toxicity  $\geq$  grade 3 lower than 10%[47]. The final aspect to consider, but not the least important, concerns the employment of immunotherapy in lung cancer treatment. Ionizing radiations can alter the tumor (beyond merely reducing the number of viable cells) and also its microenvironment, producing a specific immune response (antigenic tumoral death) that can trigger an immune response in non-irradiated sites (abscopal effect)[48]. This immunogenic effect is more pronounced with SBRT, in which high doses are delivered in few fractions[49], making this even more attractive as a treatment of OMD.

A question frequently posed in OMD is whether the better prognosis is due to the ablative treatment or the more indolent course of the disease. In a retrospective study of 90 patients with  $\leq 3$  metastases, after adjusting for factors that could potentially affect OS and PFS, it was found that patients who received local intensive treatment with CT + radiotherapy or surgery, or both, had better OS and PFS than those who received less intensive treatments, such as palliative CT alone[50]. However, randomized studies in both the general population[9,11] and in the population with EGFR mutations [46] have shown that the addition of local ablative treatment to systemic treatment is associated with increased PFS and OS.

One of the greatest remaining challenges is to distinguish between patients with OMD, characterized by a reduced number of metastases, and those with pre-widely metastatic disease, in other words, those diagnosed as having a small number of metastases but who develop multiple metastases in the following weeks or months. A search is currently underway for genetic profiles[51,52], either epigenetic modifications by overexpression or inhibition of microRNA[53,54] or methylations of genetic loci, that regulate the expression of the microRNA they encode[55]. These could possibly explain the limited rather than extensive spread of the disease in these patients. However, a greater knowledge of the immune system has revealed the importance of its interaction with the tumor for tumoral control or spread. Pitroda *et al*[56] *via* integrated transcriptional analysis, describe three molecular subtypes of liver metastases of colon cancer, all biologically different and each with a clinical course that is independent of known clinical risk factors. Canonical and stromal subtypes are characterized by a lack of, or a reduction in, T cell infiltration and the expression of non-immune inflammatory pathways, and are linked to a higher recurrence rate and a greater number of metastases. By contrast, the immune subtype, characterized by upregulation of the immune genes and a greater infiltration of T cells in the tumor, is associated with better survival, with relapse limited to between one and three metastases. These findings are in line with studies that show that the adaptive immune response plays a key role in controlling metastatic spread[57]. From these findings, it could be hypothesized that OMD would represent a point of equilibrium between tumoral growth and its inhibition by the immune system.

Over the next few years, further research into the immune and molecular profiles of OMD patients, combined with the application of radiotherapy with its immunogenic role, and treatment with new immunomodulator agents could be beneficial for these patients.

## FOOTNOTES

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## REFERENCES

- 1 **Walters S**, Maringe C, Coleman MP, Peake MD, Butler J, Young N, Bergström S, Hanna L, Jakobsen E, Kölbek K, Sundström S, Engholm G, Gavin A, Gjerstorff ML, Hatcher J, Johannesen TB, Linklater KM, McGahan CE, Steward J, Tracey E, Turner D, Richards MA, Rachet B; ICBP Module 1 Working Group. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004-2007. *Thorax* 2013; **68**: 551-564 [PMID: 23399908 DOI: 10.1136/thoraxjnl-2012-202297]
- 2 **Amin MB**, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM, Meyer LR. *AJCC Cancer Staging Manual*. Springer International Publishing; 2017: XVII, 1032
- 3 **Weichselbaum RR**, Hellman S. Oligometastases revisited. *Nat Rev Clin Oncol* 2011; **8**: 378-382 [PMID: 21423255 DOI: 10.1038/nrclinonc.2011.44]
- 4 **Hellman S**, Weichselbaum RR. Oligometastases. *J Clin Oncol* 1995; **13**: 8-10 [PMID: 7799047 DOI: 10.1200/JCO.1995.13.1.8]
- 5 **Mehta N**, Mauer AM, Hellman S, Haraf DJ, Cohen EE, Vokes EE, Weichselbaum RR. Analysis of further disease progression in metastatic non-small cell lung cancer: implications for locoregional treatment. *Int J Oncol* 2004; **25**: 1677-1683 [PMID: 15547705]
- 6 **Parikh RB**, Cronin AM, Kozono DE, Oxnard GR, Mak RH, Jackman DM, Lo PC, Baldini EH, Johnson BE, Chen AB. Definitive primary therapy in patients presenting with oligometastatic non-small cell lung cancer. *Int J Radiat Oncol Biol*

- Phys* 2014; **89**: 880-887 [PMID: [24867533](#) DOI: [10.1016/j.ijrobp.2014.04.007](#)]
- 7 **Dingemans AC**, Hendriks LEL, Berghmans T, Levy A, Hasan B, Faivre-Finn C, Gijb-levra M, Gijb-levra N, Girard N, Greillier L, Lantuéjoul S, Edwards J, O'Brien M, Reck M, Smit EF, Van Schil P, Postmus PE, Ramella S, Lievens Y, Gaga M, Peled N, Scagliotti GV, Senan S, Paz-Ares L, Guckenberger M, McDonald F, Ekman S, Cufer T, Gietema H, Infante M, Dziadziuszko R, Peters S, Porta RR, Vansteenkiste J, Doooms C, de Ruyscher D, Besse B, Novello S. Definition of Synchronous Oligometastatic Non-Small Cell Lung Cancer-A Consensus Report. *J Thorac Oncol* 2019; **14**: 2109-2119 [PMID: [31398540](#) DOI: [10.1016/j.jtho.2019.07.025](#)]
- 8 **Ashworth A**, Rodrigues G, Boldt G, Palma D. Is there an oligometastatic state in non-small cell lung cancer? *Lung Cancer* 2013; **82**: 197-203 [PMID: [24051084](#) DOI: [10.1016/j.lungcan.2013.07.026](#)]
- 9 **Gomez DR**, Tang C, Zhang J, Blumenschein GR Jr, Hernandez M, Lee JJ, Ye R, Palma DA, Louie AV, Camidge DR, Doebele RC, Skoulidis F, Gaspar LE, Welsh JW, Gibbons DL, Karam JA, Kavanagh BD, Tsao AS, Sepesi B, Swisher SG, Heymach JV. Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study. *J Clin Oncol* 2019; **37**: 1558-1565 [PMID: [31067138](#) DOI: [10.1200/JCO.19.00201](#)]
- 10 **Iyengar P**, Wardak Z, Gerber DE, Tumati V, Ahn C, Hughes RS, Dowell JE, Cheedella N, Nedzi L, Westover KD, Pulipparacharuvil S, Choy H, Timmerman RD. Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. *JAMA Oncol* 2018; **4**: e173501 [PMID: [28973074](#) DOI: [10.1001/jamaoncol.2017.3501](#)]
- 11 **Palma DA**, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, Mulroy L, Lock M, Rodrigues GB, Yaremko BP, Schellenberg D, Ahmad B, Griffioen G, Senthil S, Swaminath A, Kopeck N, Liu M, Moore K, Currie S, Bauman GS, Warner A, Senan S. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet* 2019; **393**: 2051-2058 [PMID: [30982687](#) DOI: [10.1016/S0140-6736\(18\)32487-5](#)]
- 12 **Bergsma DP**, Salama JK, Singh DP, Chmura SJ, Milano MT. Radiotherapy for Oligometastatic Lung Cancer. *Front Oncol* 2017; **7**: 210 [PMID: [28975081](#) DOI: [10.3389/fonc.2017.00210](#)]
- 13 **Ashworth AB**, Senan S, Palma DA, Riquet M, Ahn YC, Ricardi U, Congedo MT, Gomez DR, Wright GM, Melloni G, Milano MT, Sole CV, De Pas TM, Carter DL, Warner AJ, Rodrigues GB. An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. *Clin Lung Cancer* 2014; **15**: 346-355 [PMID: [24894943](#) DOI: [10.1016/j.clcc.2014.04.003](#)]
- 14 **Uppal A**, Ferguson MK, Posner MC, Hellman S, Khodarev NN, Weichselbaum RR. Towards a molecular basis of oligometastatic disease: potential role of micro-RNAs. *Clin Exp Metastasis* 2014; **31**: 735-748 [PMID: [24968866](#) DOI: [10.1007/s10585-014-9664-3](#)]
- 15 **Palma DA**, Louie AV, Rodrigues GB. New Strategies in Stereotactic Radiotherapy for Oligometastases. *Clin Cancer Res* 2015; **21**: 5198-5204 [PMID: [26626571](#) DOI: [10.1158/1078-0432.CCR-15-0822](#)]
- 16 **Couñago F**, Luna J, Guerrero LL, Vaquero B, Guillén-Sacoto MC, González-Merino T, Taboada B, Díaz V, Rubio-Viqueira B, Díaz-Gavela AA, Marcos FJ, Del Cerro E. Management of oligometastatic non-small cell lung cancer patients: Current controversies and future directions. *World J Clin Oncol* 2019; **10**: 318-339 [PMID: [31799148](#) DOI: [10.5306/wjco.v10.i10.318](#)]
- 17 **Vallièrès E**. Oligometastatic NSCLC: the changing role of surgery. *Transl Lung Cancer Res* 2014; **3**: 192-194 [PMID: [25806300](#) DOI: [10.3978/j.issn.2218-6751.2014.06.06](#)]
- 18 **Bartlett EK**, Simmons KD, Wachtel H, Roses RE, Fraker DL, Kelz RR, Karakousis GC. The rise in metastasectomy across cancer types over the past decade. *Cancer* 2015; **121**: 747-757 [PMID: [25377689](#) DOI: [10.1002/cncr.29134](#)]
- 19 **Patchell RA**, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, Markesbery WR, Foon KA, Young B. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA* 1998; **280**: 1485-1489 [PMID: [9809728](#) DOI: [10.1001/jama.280.17.1485](#)]
- 20 **De Ruyscher D**, Wanders R, van Baardwijk A, Dingemans AM, Reymen B, Houben R, Bootsma G, Pitz C, van Eijssden L, Geraedts W, Baumert BG, Lambin P. Radical treatment of non-small-cell lung cancer patients with synchronous oligometastases: long-term results of a prospective phase II trial (Nct01282450). *J Thorac Oncol* 2012; **7**: 1547-1555 [PMID: [22982655](#) DOI: [10.1097/JTO.0b013e318262caf6](#)]
- 21 **Tönnies M**, Pfannschmidt J, Bauer TT, Kollmeier J, Tönnies S, Kaiser D. Metastasectomy for synchronous solitary non-small cell lung cancer metastases. *Ann Thorac Surg* 2014; **98**: 249-256 [PMID: [24820385](#) DOI: [10.1016/j.athoracsur.2014.03.028](#)]
- 22 **Johnson KK**, Rosen JE, Salazar MC, Boffa DJ. Outcomes of a Highly Selective Surgical Approach to Oligometastatic Lung Cancer. *Ann Thorac Surg* 2016; **102**: 1166-1171 [PMID: [27344278](#) DOI: [10.1016/j.athoracsur.2016.04.086](#)]
- 23 **Salama JK**, Hasselle MD, Chmura SJ, Malik R, Mehta N, Yenice KM, Villafior VM, Stadler WM, Hoffman PC, Cohen EE, Connell PP, Haraf DJ, Vokes EE, Hellman S, Weichselbaum RR. Stereotactic body radiotherapy for multisite extracranial oligometastases: final report of a dose escalation trial in patients with 1 to 5 sites of metastatic disease. *Cancer* 2012; **118**: 2962-2970 [PMID: [22020702](#) DOI: [10.1002/cncr.26611](#)]
- 24 **De Ruyscher D**, Wanders R, Hendriks LE, van Baardwijk A, Reymen B, Houben R, Bootsma G, Pitz C, van Eijssden L, Dingemans AC. Progression-Free Survival and Overall Survival Beyond 5 Years of NSCLC Patients With Synchronous Oligometastases Treated in a Prospective Phase II Trial (NCT 01282450). *J Thorac Oncol* 2018; **13**: 1958-1961 [PMID: [30253974](#) DOI: [10.1016/j.jtho.2018.07.098](#)]
- 25 **Gomez DR**, Blumenschein GR Jr, Lee JJ, Hernandez M, Ye R, Camidge DR, Doebele RC, Skoulidis F, Gaspar LE, Gibbons DL, Karam JA, Kavanagh BD, Tang C, Komaki R, Louie AV, Palma DA, Tsao AS, Sepesi B, William WN, Zhang J, Shi Q, Wang XS, Swisher SG, Heymach JV. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *Lancet Oncol* 2016; **17**: 1672-1682 [PMID: [27789196](#) DOI: [10.1016/S1470-2045\(16\)30532-0](#)]
- 26 **De Rose F**, Cozzi L, Navarria P, Ascolese AM, Clerici E, Infante M, Alloisio M, Testori A, Toschi L, Finocchiaro G,

- Santoro A, Scorsetti M. Clinical Outcome of Stereotactic Ablative Body Radiotherapy for Lung Metastatic Lesions in Non-small Cell Lung Cancer Oligometastatic Patients. *Clin Oncol (R Coll Radiol)* 2016; **28**: 13-20 [PMID: [26385822](#) DOI: [10.1016/j.clon.2015.08.011](#)]
- 27 Inoue T, Katoh N, Aoyama H, Onimaru R, Taguchi H, Onodera S, Yamaguchi S, Shirato H. Clinical outcomes of stereotactic brain and/or body radiotherapy for patients with oligometastatic lesions. *Jpn J Clin Oncol* 2010; **40**: 788-794 [PMID: [20406944](#) DOI: [10.1093/jcco/hyq044](#)]
- 28 Hasselle MD, Haraf DJ, Rusthoven KE, Golden DW, Salgia R, Villaflor VM, Shah N, Hoffman PC, Chmura SJ, Connell PP, Vokes EE, Weichselbaum RR, Salama JK. Hypofractionated image-guided radiation therapy for patients with limited volume metastatic non-small cell lung cancer. *J Thorac Oncol* 2012; **7**: 376-381 [PMID: [22198429](#) DOI: [10.1097/JTO.0b013e31824166a5](#)]
- 29 Collen C, Christian N, Schallier D, Meysman M, Duchateau M, Storme G, De Ridder M. Phase II study of stereotactic body radiotherapy to primary tumor and metastatic locations in oligometastatic nonsmall-cell lung cancer patients. *Ann Oncol* 2014; **25**: 1954-1959 [PMID: [25114022](#) DOI: [10.1093/annonc/mdl370](#)]
- 30 Wujanto C, Vellayappan B, Siva S, Louie AV, Guckenberger M, Slotman BJ, Onishi H, Nagata Y, Liu M, Lo SS. Stereotactic Body Radiotherapy for Oligometastatic Disease in Non-small Cell Lung Cancer. *Front Oncol* 2019; **9**: 1219 [PMID: [31799188](#) DOI: [10.3389/fonc.2019.01219](#)]
- 31 Simon CJ, Dupuy DE, DiPetrillo TA, Safran HP, Grieco CA, Ng T, Mayo-Smith WW. Pulmonary radiofrequency ablation: long-term safety and efficacy in 153 patients. *Radiology* 2007; **243**: 268-275 [PMID: [17392258](#) DOI: [10.1148/radiol.2431060088](#)]
- 32 Picchi SG, Lassandro G, Bianco A, Coppola A, Ierardi AM, Rossi UG, Lassandro F. RFA of primary and metastatic lung tumors: long-term results. *Med Oncol* 2020; **37**: 35 [PMID: [32219567](#) DOI: [10.1007/s12032-020-01361-1](#)]
- 33 Maiwand MO, Asimakopoulos G. Cryosurgery for lung cancer: clinical results and technical aspects. *Technol Cancer Res Treat* 2004; **3**: 143-150 [PMID: [15059020](#) DOI: [10.1177/153303460400300207](#)]
- 34 Seijo LM, Sterman DH. Interventional pulmonology. *N Engl J Med* 2001; **344**: 740-749 [PMID: [11236779](#) DOI: [10.1056/NEJM200103083441007](#)]
- 35 Ernst A, Silvestri GA, Johnstone D; American College of Chest Physicians. Interventional pulmonary procedures: Guidelines from the American College of Chest Physicians. *Chest* 2003; **123**: 1693-1717 [PMID: [12740291](#) DOI: [10.1378/chest.123.5.1693](#)]
- 36 Bolliger CT, Mathur PN, Beamis JF, Becker HD, Cavaliere S, Colt H, Diaz-Jimenez JP, Dumon JF, Edell E, Kovitz KL, Macha HN, Mehta AC, Marel M, Noppen M, Strausz J, Sutedja TG; European Respiratory Society/American Thoracic Society. ERS/ATS statement on interventional pulmonology. European Respiratory Society/American Thoracic Society. *Eur Respir J* 2002; **19**: 356-373 [PMID: [11866017](#) DOI: [10.1183/09031936.02.00204602](#)]
- 37 Harris K, Puchalski J, Sterman D. Recent Advances in Bronchoscopic Treatment of Peripheral Lung Cancers. *Chest* 2017; **151**: 674-685 [PMID: [27292045](#) DOI: [10.1016/j.chest.2016.05.025](#)]
- 38 Wang H, Littrup PJ, Duan Y, Zhang Y, Feng H, Nie Z. Thoracic masses treated with percutaneous cryotherapy: initial experience with more than 200 procedures. *Radiology* 2005; **235**: 289-298 [PMID: [15798173](#) DOI: [10.1148/radiol.2351030747](#)]
- 39 Bang HJ, Littrup PJ, Currier BP, Goodrich DJ, Aoun HD, Klein LC, Kuo JC, Heilbrun LK, Gadgeel S, Goodman AC. Percutaneous cryoablation of metastatic lesions from non-small-cell lung carcinoma: initial survival, local control, and cost observations. *J Vasc Interv Radiol* 2012; **23**: 761-769 [PMID: [22626267](#) DOI: [10.1016/j.jvir.2012.02.013](#)]
- 40 Schanne DH, Heitmann J, Guckenberger M, Andrasschke NHJ. Evolution of treatment strategies for oligometastatic NSCLC patients - A systematic review of the literature. *Cancer Treat Rev* 2019; **80**: 101892 [PMID: [31522079](#) DOI: [10.1016/j.ctrv.2019.101892](#)]
- 41 Fleckenstein J, Petroff A, Schäfers HJ, Wehler T, Schöpe J, Rübe C. Long-term outcomes in radically treated synchronous vs. metachronous oligometastatic non-small-cell lung cancer. *BMC Cancer* 2016; **16**: 348 [PMID: [27255302](#) DOI: [10.1186/s12885-016-2379-x](#)]
- 42 Bertolaccini L, Pardolesi A, Forti Parri SN, Bonfanti B, Brandolini J, Solli P. Surgical approaches in patients with oligometastatic non-small cell lung cancer. *J Thorac Dis* 2018; **10**: 498-502 [PMID: [29600084](#) DOI: [10.21037/jtd.2017.11.135](#)]
- 43 Baker S, Dahele M, Lagerwaard FJ, Senan S. A critical review of recent developments in radiotherapy for non-small cell lung cancer. *Radiat Oncol* 2016; **11**: 115 [PMID: [27600665](#) DOI: [10.1186/s13014-016-0693-8](#)]
- 44 Albain KS, Swann RS, Rusch VW, Turrisi AT 3rd, Shepherd FA, Smith C, Chen Y, Livingston RB, Feins RH, Gandara DR, Fry WA, Darling G, Johnson DH, Green MR, Miller RC, Ley J, Sause WT, Cox JD. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet* 2009; **374**: 379-386 [PMID: [19632716](#) DOI: [10.1016/S0140-6736\(09\)60737-6](#)]
- 45 Eberhardt WE, Pöttgen C, Gauler TC, Friedel G, Veit S, Heinrich V, Welter S, Budach W, Spengler W, Kimmich M, Fischer B, Schmidberger H, De Ruyscher D, Belka C, Cordes S, Hepp R, Lütke-Brintrup D, Lehmann N, Schuler M, Jöckel KH, Stamatis G, Stuschke M. Phase III Study of Surgery Versus Definitive Concurrent Chemoradiotherapy Boost in Patients With Resectable Stage IIIA(N2) and Selected IIIB Non-Small-Cell Lung Cancer After Induction Chemotherapy and Concurrent Chemoradiotherapy (ESPAUE). *J Clin Oncol* 2015; **33**: 4194-4201 [PMID: [26527789](#) DOI: [10.1200/JCO.2015.62.6812](#)]
- 46 Wang X, Zeng M. First-line tyrosine kinase inhibitor with or without aggressive upfront local radiation therapy in patients with EGFRm oligometastatic non-small cell lung cancer: Interim results of a randomized phase III, open-label clinical trial (SINDAS) (NCT02893332). *JCO* 2020; **38**: 9508 [DOI: [10.1200/JCO.2020.38.15\\_suppl.9508](#)]
- 47 Iyengar P, Lau S, Donington JS, Suh RD. Local Therapy for Limited Metastatic Non-Small Cell Lung Cancer: What Are the Options and Is There a Benefit? *Am Soc Clin Oncol Educ Book* 2016; **35**: e460-e467 [PMID: [27249754](#) DOI: [10.1200/EDBK\\_158734](#)]
- 48 Formenti SC, Demaria S. Systemic effects of local radiotherapy. *Lancet Oncol* 2009; **10**: 718-726 [PMID: [19573801](#) DOI: [10.1016/S1470-2045\(09\)70082-8](#)]

- 49 **Schaue D**, Ratikan JA, Iwamoto KS, McBride WH. Maximizing tumor immunity with fractionated radiation. *Int J Radiat Oncol Biol Phys* 2012; **83**: 1306-1310 [PMID: [22208977](#) DOI: [10.1016/j.ijrobp.2011.09.049](#)]
- 50 **Sheu T**, Heymach JV, Swisher SG, Rao G, Weinberg JS, Mehran R, McAleer MF, Liao Z, Aloia TA, Gomez DR. Propensity score-matched analysis of comprehensive local therapy for oligometastatic non-small cell lung cancer that did not progress after front-line chemotherapy. *Int J Radiat Oncol Biol Phys* 2014; **90**: 850-857 [PMID: [25216859](#) DOI: [10.1016/j.ijrobp.2014.07.012](#)]
- 51 **Iacobuzio-Donahue CA**, Fu B, Yachida S, Luo M, Abe H, Henderson CM, Vilardell F, Wang Z, Keller JW, Banerjee P, Herman JM, Cameron JL, Yeo CJ, Halushka MK, Eshleman JR, Raben M, Klein AP, Hruban RH, Hidalgo M, Laheru D. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. *J Clin Oncol* 2009; **27**: 1806-1813 [PMID: [19273710](#) DOI: [10.1200/JCO.2008.17.7188](#)]
- 52 **Turajlic S**, Xu H, Litchfield K, Rowan A, Chambers T, Lopez JI, Nicol D, O'Brien T, Larkin J, Horswell S, Stares M, Au L, Jamal-Hanjani M, Challacombe B, Chandra A, Hazell S, Eichler-Jonsson C, Soultati A, Chowdhury S, Rudman S, Lynch J, Fernando A, Stamp G, Nye E, Jabbar F, Spain L, Lall S, Guarch R, Falzon M, Proctor I, Pickering L, Gore M, Watkins TBK, Ward S, Stewart A, DiNatale R, Becerra MF, Reznik E, Hsieh JJ, Richmond TA, Mayhew GF, Hill SM, McNally CD, Jones C, Rosenbaum H, Stanislaw S, Burgess DL, Alexander NR, Swanton C; PEACE; TRACERx Renal Consortium. Tracking Cancer Evolution Reveals Constrained Routes to Metastases: TRACERx Renal. *Cell* 2018; **173**: 581-594.e12 [PMID: [29656895](#) DOI: [10.1016/j.cell.2018.03.057](#)]
- 53 **Lussier YA**, Khodarev NN, Regan K, Corbin K, Li H, Ganai S, Khan SA, Gnerlich JL, Darga TE, Fan H, Karpenko O, Paty PB, Posner MC, Chmura SJ, Hellman S, Ferguson MK, Weichselbaum RR. Oligo- and polymetastatic progression in lung metastasis(es) patients is associated with specific microRNAs. *PLoS One* 2012; **7**: e50141 [PMID: [23251360](#) DOI: [10.1371/journal.pone.0050141](#)]
- 54 **Lussier YA**, Xing HR, Salama JK, Khodarev NN, Huang Y, Zhang Q, Khan SA, Yang X, Hasselle MD, Darga TE, Malik R, Fan H, Perakis S, Filippo M, Corbin K, Lee Y, Posner MC, Chmura SJ, Hellman S, Weichselbaum RR. MicroRNA expression characterizes oligometastasis(es). *PLoS One* 2011; **6**: e28650 [PMID: [22174856](#) DOI: [10.1371/journal.pone.0028650](#)]
- 55 **Oshima G**, Poli EC, Bolt MJ, Chlenski A, Forde M, Jutzy JMS, Biyani N, Posner MC, Pitroda SP, Weichselbaum RR, Khodarev NN. DNA Methylation Controls Metastasis-Suppressive 14q32-Encoded miRNAs. *Cancer Res* 2019; **79**: 650-662 [PMID: [30538122](#) DOI: [10.1158/0008-5472.CAN-18-0692](#)]
- 56 **Pitroda SP**, Khodarev NN, Huang L, Uppal A, Wightman SC, Ganai S, Joseph N, Pitt J, Brown M, Forde M, Mangold K, Xue L, Weber C, Segal JP, Kadri S, Stack ME, Khan S, Paty P, Kaul K, Andrade J, White KP, Talamonti M, Posner MC, Hellman S, Weichselbaum RR. Integrated molecular subtyping defines a curable oligometastatic state in colorectal liver metastasis. *Nat Commun* 2018; **9**: 1793 [PMID: [29728604](#) DOI: [10.1038/s41467-018-04278-6](#)]
- 57 **Van den Eynde M**, Mlecnik B, Bindea G, Fredriksen T, Church SE, Lafontaine L, Haicheur N, Marliot F, Angelova M, Vasaturo A, Bruni D, Jouret-Mourin A, Baldin P, Huyghe N, Haustermans K, Debucquoy A, Van Cutsem E, Gigot JF, Hubert C, Kartheuser A, Remue C, Léonard D, Valge-Archer V, Pagès F, Machiels JP, Galon J. The Link between the Multiverse of Immune Microenvironments in Metastases and the Survival of Colorectal Cancer Patients. *Cancer Cell* 2018; **34**: 1012-1026.e3 [PMID: [30537506](#) DOI: [10.1016/j.ccell.2018.11.003](#)]



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