Review Article

The Role of Local Treatment in Oligometastatic and Oligoprogressive Cancer

Jan Haussmann*, Christiane Matuschek*, Edwin Bölke, Klaus Orth, Pirus Ghadjar, Wilfried Budach

Summary

Background: Systemic treatment is standard for most types of cancer with disseminated metastases. The role of local treatment (LT) of individual tumor foci in patients with oligometastatic disease is unclear and the object of current scientific studies.

Methods: This review is based on pertinent publications retrieved by a selective search in PubMed.

Results: Four randomized trials have shown that radical local treatment confers an advantage with respect to overall survival (OS), compared to systemic treatment alone, in patients with oligometastatic disease. In patients with synchronous metastases and a stable primary tumor, LT prolongs the median overall survival by approximately two years. A single randomized trial for oligometastatic small-cell lung cancer did not show any prolongation of overall survival. Local treatment increased the frequency of grade III side effects by approximately 10%.

Conclusion: Although local treatment already has a place in many guidelines on the basis of the findings of a small number of prospective and retrospective studies, a number of questions remain open. At present, the option of local treatment should be considered by an interdisciplinary tumor board individually for suitable patients.

Cite this as

Haussmann J, Matuschek C, Bölke E, Orth K, Ghadjar P, Budach W: The role of local treatment in oligometastatic and oligoprogressive cancer. *Dtsch Arztebl Int* 2019; 116: 849–56. DOI: 10.3238/arztebl.2019.0849

The majority of patients with metastatic cancer cannot be cured by systemic treatment. The question remains open as to whether the removal of individual tumor lesions alters the disease course. The practice of radical removal of limited metastases recommended in many guidelines is based on large patient series with unexpectedly good oncological outcomes. However, it is unclear whether this is due to selected, favorable tumor biology or to local treatment (LT).

In 1995, Hellman and Weichselbaum postulated for the first time the existence of an interim stage between limited local disease that can be cured by LT and a disseminated incurable stage (1). It may be possible to successfully treat patients by means of LT in this interim stage of “oligometastatic disease.” A further rationale for local treatment is based on the results of autopsy studies demonstrating that new metastases form from existing metastases. Disrupting this cascade could reduce—or even completely eliminate—the rate of metastatic disease (2).

Since clear definitions on oligometastatic disease are lacking, expert groups met regularly for the purposes of consensus-finding; thus, for example, oligometastatic disease in non-small-cell lung cancer (NSCLC) was restricted to a stage at which a maximum of five metastases in a maximum of three organs are present (3). As in the S3 guideline on lung cancer, intensive diagnostic investigations to determine metastatic spread are recommended, including magnetic resonance brain imaging and positron emission computed tomography (PET-CT) for the purposes of staging.

An important prognostic factor is seen in the distinction between the development of metastasis at the same time as the primary tumor (synchronous) or after the primary tumor (metachronous) (*Figure 1*).

With the advent of more sparing local treatments, such as minimally invasive surgical techniques, stereotactic radiotherapy (SRT), and radiofrequency ablation (RFA), greater interest has been shown in prospective studies in the evaluation of local therapies. In addition, continuous improvements in systemic treatment, such as the integration of immune checkpoint inhibitors, have led to an improvement in systemic control and survival time.

* Jan Haussmann and Christiane Matuschek share first authorship.

Department of Radiation Oncology, Düsseldorf University Hospital, Heinrich-Heine-Universität Düsseldorf: Dr. med. Jan Haussmann, PD Dr. med. Christiane Matuschek, Prof. Dr. med. Edwin Bölke, Prof. Dr. med. Wilfried Budach

Goslar: Prof. Dr. med. Klaus Orth (formerly: Department of General, Visceral and Thoracic Surgery, Asklepios Harzkliniken Goslar)

Department of Radiation Oncology and Radiotherapy, Charité—Universitätsmedizin Berlin: Prof. Dr. med. Pirus Ghadjar

FIGURE 1

Schematic representation of various concepts of metastatic disease

Left: Synchronous oligometastatic disease: simultaneous occurrence of primary tumor (rectangle) and metastases (circle).

Center: Metachronous oligometastatic disease: the metastases (circle) occur subsequent to a controlled primary tumor (green rectangle).

Right: Oligoprogession: systemic treatment controls primary tumor (green rectangle) and metastases (green circle). Isolated metastases fail to respond (red circle).

In principle, there are two possible approaches to the integration of local ablative treatment in patients with metastatic disease. On the one hand, local treatment could be carried out following systemic therapy in the form of consolidative treatment. The aim here is to delay or prevent the development of new metastases. Alternatively, LT could be used as a primary metastasis-specific treatment in order to halt further spread of disseminated disease. This could delay or, under certain circumstances, even eliminate the need for systemic treatment (*Figure 2*).

LT is an established standard in the treatment of brain metastasis in the setting of oligo- and polymetastatic disease. A number of randomized studies have shown that aggressive local treatment of metastatic cancer is able to prolong survival compared to whole brain radiation therapy alone (4–7).

Oligoprogession represents another clinical setting in which the use of local treatment is discussed. This refers to the recurrence of disease in a patient undergoing systemic treatment that has a small number of new, progressive, or insufficiently responsive lesions, this being interpreted as an indication of intratumoral heterogeneity. The aim of local ablative treatment in oligoprogession is to eliminate the cell

clones that are no longer responding to treatment in order to continue systemic therapy (*Figure 2*). The expression was first used in the context of targeted drug therapy of lung cancer with molecular EGFR, ALK, or ROS1 mutations or translocations (8). The available systemic therapy is characterized by high response rates, a comparatively mild side-effects profile, and at least equivalent overall survival compared to cytotoxic therapy. However, virtually all patients develop resistance over the course of treatment.

Methods

A selective literature search was conducted in PubMed. Studies evaluating the oncological benefits and side effects of local treatment in patients with metastatic solid tumors were sought. We identified a large number of retrospective analyses, many prospective single-arm studies, as well as a number of prospective randomized studies (n = 15). A distinction was made between the histological entity (total or individual histologies), the LT modality (surgery, ablative radiotherapy, or other), the use of LT (several organ systems or organ-specific), status of metastatic disease (poly- or oligometastasis), as well as the degree of local treatment, for example, partial treatment of the primary tumor or full treatment

FIGURE 2

Possible treatment algorithms in oligometastatic disease and oligoproggression

of all known tumor sites. Added to this is a further variable: the diagnostic method with which disease stage was determined. The higher-value evidence for local treatment options in oligometastatic disease and progression, subdivided according to histology, are presented below (Table).

Mixed histologies

In their randomized phase-II screening trial in patients with a variety of solid tumor cancers, metachronous metastasis at $\leq$ five sites, and controlled primary tumor, Palma et al. investigated whether stereotactic radiotherapy ($n = 66$) resulted in an improvement in overall survival (OS) compared to standard treatment (palliative radiotherapy and standard systemic treatment). Treatment with stereotactic radiotherapy (SRT) was able to significantly prolong the median OS from 28 to 41 months ($p = 0.09$; hazard ratio [HR] = 0.57). This outcome was attributed to a doubling of progression-free survival (PFS) ($p = 0.0012$; HR = 0.47). Quality of life was not impaired by SRT. However, there were three deaths in the SRT treatment arm that were possibly associated with the radiation therapy (9).

A series of prospective single-arm studies were also carried out. The largest of these included 147

metachronous metastasis patients with between one and five metastases that were evaluated using PET-CT and treated locally with SRT. The rate of grade-III+ toxicity was 3.4% and the 2- and 5-year survival rates (YSR) were 45% and 43%, respectively (10). Other studies reported a PFS of 5–11 months and 5-YSR of 30–42% (11, 12, 13–16).

Lung cancer

A meta-analysis based on individual patient data showed that local treatment in oligometastatic patients with non-small-cell lung cancer was able to achieve a 5-YSR of approximately 30% (17, 18). Prognostic factors here included the time of metastatic spread within the disease course (syn- or metachronous), nodal status, and the histological subtype (17). Other studies identified general condition, number and size of metastases, as well as the use of LT as factors influencing prognosis (19, 20).

Two randomized phase-II studies have since shown that local treatment (primarily radiotherapy in both studies) in synchronous metastatic disease following adequate systemic treatment and stable primary tumor with a maximum of three other lesions results in a doubling of progression-free survival (9.7 vs. 3.5

TABLE

Prospective studies on local treatment of oligometastatic cancer

First author, year	Histology	n	FU (months)	Systemic therapy	LT organ	n Met	Syn/metachronous metastasis (%)	Treatment arm	Toxicity = grade III	Median PFS (months)	Median OS (months)	Additional endpoints
Randomized studies												
Palma 2018 (9)	Mixed	99	27	SOC	MO	1–5	0/100	SOC + SRT	≥ II: 29%	12*	41*	5-YSR = 46%*
								SOC	≥ II: 9%*	6	28	5-YSR = 24%
Gomez 2016, 2019 (22, 24)	NSCLC	49	18.7	CTx/TKI	MO	1–3	94/6	RT, SRT, SR + MainTx/Obs	20%	14.2*	41.2*	New Mets after 14.2 months
								MainTx/Obs	8.3%	4.4	17	New Mets after 6 months
Iyengar 2018 (21)	NSCLC	29	9.6	CTx	MO	1–3	100/0	SRT + MainTx/Obs	28.6%	9.7*	NA	
								MainTx/Obs	20.0%	3.5	NA	
Ruers 2017 (40)	CRC	119	116.4	FOLFOX 4	Hep	1–9	38/62	RFA + SR + CTx	0%	16.8*	45.6*	8-YSR = 35.9%*
								CTx	0%	9.9	40.5	8-YSR = 8.9%
Ost 2018 (30)	PC	62	36	No	MO	1–3	0/100	SRT, SR	0%	NA	NA	ADT-free S: 21 months*
								Obs	0%	NA	NA	ADT-free S: 13 months
Parker 2018 (33)	PC	2 061	37	ADT + Doc	Prostate	< 4	100/0	RT + SOC (LMB)	5%	~36*	49.1*	3-YSR = 81%*
Prespecified subgroup LMB		LMB: 819						SOC (LMB)	1%	~22	45.4	3-YSR = 73%
Gore 2017 (29)	SCLC	97	9	CTx	MO	1–4	NA	PCI + RT	36.4%	NA	13.8	1-YSR = 50.8%
								PCI	23.8%	NA	15.8	1-YSR = 60.1%
Prospective single-arm studies												
Aujila 2019 (13)	Mixed	82	20.4	No	MO	1–5	Both	SRT	1%	8	22	10-YSR = 7.3%
Nuytens 2015 (14)	Mixed	30	36	No	MO	1–5	NA	SRT	16.7%	8	38.4	4-YSR = 38%
Milano 2012 (15)	Mixed	121	54	No	MO	1–5	Both	SRT	0.8%	11	~30	6-YSR = 20%
Salama 2012 (16)	Mixed	61	20.9	Only ADT	MO	1–5	NA	SRT	9.0%	5.1	NR	2-YSR = 56.7%
Sutera 2019 (10)	Mixed	147	41.3	No	MO	1–5	0/100	SRT	3.4%	NA	42.3	5-YSR = 43%
Wong 2016 (12)	Mixed	61	81.6	ADT	MO	1–5	NA	SRT	9.8%	5.3	28.8	5-YSR = 32%
Beckurts 1997 (e28)	CRC	126	46	No	Hep	1–6	47/53	SR	NA	NA	~26	5-YSR = 14%
Figueras 2001 (e29)	CRC	235	20	55% CTx	Hep	1–12	35/65	SR	NA	~15	40	5-YSR = 36%
Arrieta 2019 (e30)	NSCLC	37	32.5	Yes	MO	1–5	100/0	SR, RT, SRT, RFA	24%	23.5	NR	3-YSR = 60%
Collen 2014 (e31)	NSCLC	26	16.4	Yes	MO	1–5	Both	SRT	8%	11.2	23	1-YSR = 45%
De Ruysscher 2012 (e32)	NSCLC	39	27.7	95% CTx	MO	1–5	NA	SR, RT, SRT	18.0%	12.1	13.5	3-YSR = 17.5%
Endo 2014 (e33)	NSCLC	20	54.4	45% CTx	MO	1–3	50/50	SR, SRT	NA	NA	51.6	5-YSR = 44.7%
Iyengar 2014 (e34)	NSCLC	24	16.8	Sunitinib	MO	1–5	Oligopression	SRT	41.0%	14.7	20.4	3-YSR = 25%
Petty 2018 (e35)	NSCLC	29	24.2	CTx	MO	1–5	100/0	SRT	11.2%	11.2	28.4	5-YSR = 22%
Siva 2018 (32)	PC	33	24	33% ADT	MO	1–3	0/100	SRT	3.0%	NA	NR	2-YSR = 100%
Trovo 2018 (e36)	BC	54	30.0	Permitted	MO	1–5	0/100	SRT	0.0%	~29	NR	2-YSR = 95%

* Statistically significant difference to comparison group: ADT, androgen-deprivation therapy; BC, breast cancer; CRC, colorectal cancer; CTx, chemotherapy; Doc, docetaxel; FU, median or mean follow-up period; Hep, liver; YSR, year survival rate; LMB, low metastatic burden; LT, local treatment; MainTx, maintenance therapy; Mets, metastases; MO, multiple organs; n, number; NR, not reached; NSCLC, non-small-cell lung cancer; NA, not available; Obs, observation; OS, overall survival; PC, prostate cancer; PCI, prophylactic cranial irradiation; PFS, progression-free survival; RFA, radiofrequency ablation; RT, radiotherapy; S, survival; SR, surgical resection; SOC, standard of care; SRT, stereotactic radiotherapy; TKI, tyrosine kinase inhibitors.

months and 14.2 vs. 4.4 months) (21–23). A significant prolongation of median overall survival of approximately 2 years has also been demonstrated (24). In addition, the study conducted by Gomez et al. showed for the first time that local treatment reduced or delayed the development of new metastases (22). This treatment approach is now being evaluated in several large randomized phase-III trials (25). The current US guideline issued by the National Comprehensive Cancer Network (NCCN) recommends systemic treatment and local therapy in selected patients with metastatic disease involving between three and five lesions and low tumor burden (26).

Extending local treatment in small-cell lung cancer to all lesions beyond the established concepts of prophylactic cranial irradiation (PCI) (27) and consolidative thoracic radiotherapy of the primary tumor and lymph nodes (28) in a small randomized study in advanced tumors following chemotherapy conferred no survival benefit compared to PCI alone (29).

Prostate cancer

The results of two small randomized studies showed that, in contrast to observation, SRT of all metachronous metastases delays the time to initiation of androgen-deprivation therapy (ADT) by on average 8 months or reduces the percentage of patients that experience disease progression after 6 months from 67% to 29% (30, 31).

A single-arm prospective study with local treatment in 33 participants showed that a third of treated patients experienced no disease progression and 48% of patients that did not receive ADT still required no ADT after 2 years. No change in quality of life was observed (32).

Radical radiation therapy of the primary tumor represents a useful option in metastatic disease. The pooled results from two randomized studies demonstrated a significant survival benefit of 70–77% in oligometastatic patients (less than five bone lesions on conventional imaging) for prostate radiation after 3 years compared to ADT alone (33–35). According to the NCCN guideline, this represents a potential standard treatment for synchronous metastatic hormone-sensitive tumors (36).

Colorectal cancer

According to the current German S3 guideline, surgery is the recommended procedure for resectable and prognostically favorable liver metastases (37). This long-established practice is based on numerous retrospective and single-arm prospective case series in which long disease-free intervals and, in some patients, long-term cure was achieved (38).

A randomized phase-II study was able to show for the first time that additional local treatment using radiofrequency ablation with optional subsequent resection better controlled liver metastatic disease in patients with solitary non-resectable liver metastases compared to chemotherapy alone (39). The

recurrence pattern was altered in such a way that the liver recurrence rate was reduced and extra-hepatic recurrence remained at the same level. This effect translated into a significant prolongation of median PFS by 7 months in absolute terms and an increase in the 5 YSR from 30.3% to 43.1%, with approximately 20% long-term survival (40).

Additional chemotherapy in patients that have undergone complete resection of liver metastases has not demonstrated a clear survival benefit as yet (e1, e2).

Breast cancer

The efficacy of systemic treatment options in metastatic breast cancer makes these the method of choice even in limited metastatic disease. In their retrospective study, Dorn et al. showed that, even in disseminated breast cancer, oligometastatic disease responds better to treatment and, therefore, has a better prognosis compared to polymetastatic disease (e3). In terms of prospective studies, only single-arm investigations on the additional use of local treatment are available. Metastatic resection can achieve a 15-year survival rate of 26% in patients with a complete resection, a disease-free interval of at least 3 years, and a solitary metastasis (e4). A decade of recurrence-free survival is untypical for metastatic patients with systemic treatment only. Greenberg et al. showed that 1.6% of female patients with complete remission remained disease-free at 15 years (e5).

Matched-pair analyses (e6, e7) also point to a survival benefit for the use of local treatment. The matched-pair analysis in (e7) is non-significant by only a narrow margin. Ultimately, efficacy compared to systemic treatment alone is unclear, explaining why a potential survival benefit is being investigated in a randomized study (e8). The German S3 guideline and the European ESMO Guidelines recommend an individual and interdisciplinary assessment of a multimodal approach with curative intent in selected oligometastatic patients (e9, e10).

Oligoprogression

The targeted treatment of lung cancer with activating mutations results in the development of resistance in the majority of cases. Compared to switching systemic treatment, local treatment of individual radiologically measurable lesions was able to prolong progression-free survival in retrospective case series (e11–e18). A matched-pair analysis yielded evidence that local therapy and the continuation of tyrosine kinase inhibitor therapy can prolong overall survival compared to switching to cytotoxic treatment (28.2 vs. 14.7 months) (e11). Furthermore, a retrospective analysis (n = 145) suggested that consolidative LT of all metastatic sites and the primary tumor can result in an improvement in OS compared to partial LT or no LT at all (40.9; 34.1 and 30.8 months ; $p < 0.001$). The percentage of radiotherapy-related grade-III adverse events was around 25% (e14). The NCCN and ESMO guidelines

Schematic representation of the spectrum of metastatic cancer with varying biological behavior and its effect on the success of local treatment

FIGURE 3

recommend an assessment of LT as the first option in the case of a limited number of progressive lesions (26, e19).

Discussion

The results of a number of heterogeneous randomized studies with predominantly small case numbers, as well as the analysis of prospective and retrospective data collections, indicate that local ablative therapy in oligometastatic patients can improve progression-free survival and overall survival in a variety of tumor entities compared to systemic treatment alone (*Table*). The best available evidence is on non-small-cell lung cancer and colorectal cancer.

Local control appears to be equivalent, whether by means of surgical resection or radiotherapy (e20, e21). However, surgery enables histological analysis of the resected tissue, whereas radiotherapy is better established prospectively and, as a non-invasive technique, has a low rate of side effects (e22). However, severe toxicity was reported in the case of lesions in the hilum of the lung, in a paraesophageal location, or immediately adjacent to the bowel (11, e23). The presented prospective data show an increase in cumulative grade-III side effects of approximately 10% at an incidence of around 13%. LT does not appear to impair quality of life (9, 10).

The evidence on oligoprogession under systemic treatment is not so good. A number of case series showed a benefit for additional LT in unchanged systemic treatment compared to a switch in systemic treatment (8, e11–e16, e24).

However, many questions on detail remain unanswered and are the subject of ongoing studies:

- Which patients derive the greatest benefit from local treatment?
- What is the minimum number of metastases beyond which local treatment becomes unhelpful?
- What is the ideal treatment sequence and which is the ideal local treatment?
- Is partial treatment of the tumor burden helpful?
- Should systemic treatment always be carried out, or can local treatment alone be sufficient?
- Can multicenter phase-III trials confirm a clear survival benefit for local treatment without increased toxicity?

When making decisions, physicians currently find themselves in a problematic area of conflict. On the one hand, local treatment represents a treatment standard in some diseases on the basis of scientifically suboptimal evidence. Furthermore, small randomized studies that report an improvement in OS due to LT are now emerging. The number of participants in some of these studies is also limited due to the fact that the studies needed to be discontinued early due to the considerable effect of LT, and it was deemed not ethically justifiable to continue. Due to the small patient populations, however, large confirmatory studies were initiated for some diseases in order to be able to establish LT as standard treatment in the future. Many guidelines already classify LT as a treatment option, despite not always providing a clear distinction.

A further component that could change how this problem is seen is the increasing biological understanding of metastatic disease. The course of disseminated cancer is increasingly being seen as a spectrum that may lie between the extremes of long-standing stability and rapid progression (*Figure 3*). Despite the promising approaches, the majority of selected and treated patients experience recurrence. So which criteria can be used to identify patients with favorable tumor biology that would benefit from LT? Selection strategies to date have been based on clinically measurable parameters, such as tumor stage, general condition, and the time at which metastases develop. The biology of cancer was already a central aspect of assessing disease course in Hellman and Weichselbaum's hypothesis (1). A number of different working groups showed that molecular markers, such as microRNAs (12, e25) and circulating tumor cells (e26), are of prognostic value and may be able to help identify patients with favorable tumor biology. Furthermore, it has been shown for colorectal cancer that, by combining biological and clinical factors, a new classification may be possible, thereby enabling better patient selection (e27). Overall, oligometastasis or oligoprogession appear to represent only one part of a broad spectrum of metastatic cancer.

In terms of routine patient consultation, we suggest that each case be considered on an individual basis. The prognostic parameters should be assessed (good

general condition, long disease-free interval, favorable tumor biology, low tumor burden) and the options individually discussed in a multidisciplinary conference at a tumor center with appropriate expertise. Patients should then be informed about the possible advantages and disadvantages, as well as the scientific uncertainties, of local treatment. Treatment should preferably be performed in the context of clinical trials. If this is not possible, treatment based on published prospective trials and the guidelines is recommended.

Conflict of interests

The authors state that there are no conflicts of interest.

Manuscript submitted on 9 May 2019, revised version accepted on 23 September 2019

Translated from the original German by Christine Rye.

References

1. Hellman S, Weichselbaum RR: Oligometastases. *J Clin Oncol* 1995; 13: 8–10.
2. Gudem G, Van Loo P, Kremeyer B, et al.: The evolutionary history of lethal metastatic prostate cancer. *Nature* 2015; 520: 353–7.
3. Dingemans AC, Hendriks LEL, Berghmans T, et al.: Definition of synchronous oligo-metastatic non-small cell lung cancer – a consensus report. *J Thorac Oncol* 2019. doi.org/10.1016/j.jtho.2019.07.025 (epub ahead of print).
4. Patchell RA, Tibbs PA, Walsh JW, et al.: A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 1990; 322: 494–500.
5. Vecht CJ, Haaxma-Reiche H, Noordijk EM, et al.: Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? *Ann Neurol* 1993; 33: 583–90.
6. Andrews DW, Scott CB, Sperduto PW, et al.: Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* 2004; 363: 1665–72.
7. Noordijk EM, Vecht CJ, Haaxma-Reiche H, et al.: The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. *Int J Radiat Oncol Biol Phys* 1994; 29: 711–7.
8. Weickhardt AJ, Scheier B, Burke JM, et al.: Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. *J Thorac Oncol* 2012; 7: 1807–14.
9. Palma DA, Olson RA, Harrow S, et al.: Stereotactic ablative radiation therapy for the comprehensive treatment of oligometastatic tumors (SABR-COMET): results of a randomized trial. *Int J Radiat Oncol Biol Phys* 2018; 102: S3–S4.
10. Suter P, Clump DA, Kalash R, et al.: Initial results of a multicenter phase 2 trial of stereotactic ablative radiation therapy for oligometastatic cancer. *Int J Radiat Oncol Biol Phys* 2019; 103: 116–22.
11. Timmerman R, McGarry R, Yiannoutsos C, et al.: Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006; 24: 4833–9.
12. Wong AC, Watson SP, Pitroda SP, et al.: Clinical and molecular markers of long-term survival after oligometastasis-directed stereotactic body radiotherapy (SBRT). *Cancer* 2016; 122: 2242–50.
13. Aujla KS, Katz AW, Singh DP, Okunieff P, Milano MT: Hypofractionated stereotactic radiotherapy for non-breast or prostate cancer oligo-metastases: a tail of survival beyond 10 years. *Front Oncol* 2019; 9: 111.
14. Nuytens JJ, van der Voort van Zyp NC, Verhoef C, et al.: Stereotactic body radiation therapy for oligometastases to the lung: a phase 2 study. *Int J Radiat Oncol Biol Phys* 2015; 91: 337–43.
15. Milano MT, Katz AW, Zhang H, Okunieff P: Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. *Int J Radiat Oncol Biol Phys* 2012; 83: 878–86.
16. Salama JK, Hasselle MD, Chmura SJ, et al.: 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: 2962–70.

Key messages

- The metastatic stage of solid tumor cancer should be seen as a spectrum with varying prognosis.
- A subgroup of patients with disseminated solid cancer can live longer if local treatment is integrated in their therapy.
- Modern local treatments are effective methods with low side-effect profiles.
- Current patient selection according to clinical and prognostic parameters should ideally be supplemented in the future with biological parameters.
- Due to the hitherto incomplete scientific evidence, local treatment concepts should be defined as far as possible in studies or on an individual patient basis at experienced centers in the context of interdisciplinary discussion.

17. Ashworth A, Rodrigues G, Boldt G, Palma D: Is there an oligometastatic state in non-small cell lung cancer? A systematic review of the literature. *Lung Cancer* 2013; 82: 197–203.
18. Ashworth AB, Senan S, Palma DA, et al.: An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. *Clin Lung Cancer* 2014; 15: 346–55.
19. Frost N, Tessmer A, Schmittl A, et al.: Local ablative treatment for synchronous single organ oligometastatic lung cancer – a propensity score analysis of 180 patients. *Lung Cancer* 2018; 125: 164–73.
20. Parikh RB, Cronin AM, Kozono DE, et al.: Definitive primary therapy in patients presenting with oligometastatic non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2014; 89: 880–7.
21. Iyengar P, Wardak Z, Gerber DE, et al.: Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: a phase 2 randomized clinical trial. *JAMA Oncol* 2018; 4: e173501.
22. Gomez DR, Blumenschein GR Jr, Lee JJ, et al.: 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: 1672–82.
23. Gomez DR, Tang C, Zhang J, et al.: 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: 1558–65.
24. Gomez DR, Tang C, Zhang J, et al.: 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; 0: JCO1900201.
25. Maintenance chemotherapy with or without local consolidative therapy in treating patients with stage IV non-small cell lung cancer. 2017. clinical trials.gov/ct2/show/NCT03137771 (last accessed on 2 September 2019).
26. National Comprehensive Cancer Network: Non-small cell lung cancer (Version 5.2019). www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (last accessed on 2 September 2019).
27. Slotman B, Faivre-Finn C, Kramer G, et al.: Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med* 2007; 357: 664–72.
28. Slotman BJ, van Tinteren H, Praag JO, et al.: Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. *Lancet* 2015; 385: 36–42.
29. Gore EM, Hu C, Sun AY, et al.: Randomized phase II study comparing prophylactic cranial irradiation alone to prophylactic cranial irradiation and consolidative extracranial irradiation for extensive-disease small cell lung cancer (ED SCLC): NRG Oncology RTOG 0937. *J Thorac Oncol* 2017; 12: 1561–70.
30. Ost P, Reynders D, Decaestecker K, et al.: Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. *J Clin Oncol* 2018; 36: 446–53.

31. Phillips R, Radwan N, Ross AE, et al.: Interim results of a randomized trial of observation versus SABR for castration-sensitive oligometastatic prostate cancer. *Int J of Radiat Oncol Biol Phys* 2018; 102: e134–e135.
32. Siva S, Bressel M, Murphy DG, et al.: Stereotactic ablative body radiotherapy (SABR) for oligometastatic prostate cancer: a prospective clinical trial. *Eur Urol* 2018; 74: 455–62.
33. Parker CC, James ND, Brawley CD, et al.: Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet* 2018; 392: 2353–66.
34. Boeve LMS, Hulshof M, Vis AN, et al.: Effect on survival of androgen deprivation therapy alone compared to androgen deprivation therapy combined with concurrent radiation therapy to the prostate in patients with primary bone metastatic prostate cancer in a prospective randomised clinical trial: data from the HORRAD trial. *Eur Urol* 2019; 75: 410–8.
35. Burdett S, Boeve LM, Ingleby FC, et al.: Prostate radiotherapy for metastatic hormone-sensitive prostate cancer: a STOPCAP systematic review and meta-analysis. *Eur Urol* 2019; 76 :115–24.
36. National Comprehensive Cancer Network: Prostate cancer (Version 4.19). www.nccn.org/professionals/physician_gls/pdf/prostate.pdf (last accessed on 24 August, 2019).
37. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Kolorektales Karzinom, Langversion 2.1, 2019, AWMF Registrierungsnummer: 021/007OL. www.awmf.org/uploads/tx_szleitlinien/021-007OL_S3_Kolorektales-Karzinom-KRK_2019-01.pdf (last accessed on 2 September 2019).
38. Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M: Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. *Br J Cancer* 2006; 94: 982–99.
39. Ruers T, Punt C, Van Coevorden F, et al.: Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC intergroup phase II study (EORTC 40004). *Ann Oncol* 2012; 23: 2619–26.
40. Ruers T, Van Coevorden F, Punt CJ, et al.: Local treatment of unresectable colorectal liver metastases: results of a randomized phase II trial. *J Natl Cancer Inst* 2017; 109.

Corresponding author

Prof. Dr. med. Wilfried Budach
 Ärztlicher Direktor der Klinik für Strahlentherapie und
 Radioonkologie
 Medizinische Fakultät Heinrich-Heine-Universität Düsseldorf
 Moorenstrasse 5
 40225 Düsseldorf, Germany
wilfried.budach@med.uni-duesseldorf.de

Cite this as

Hausmann J, Matuschek C, Bölke E, Orth K, Ghadjar P, Budach W:
 The role of local treatment in oligometastatic and oligoprogressive cancer.
Dtsch Arztebl Int 2019; 116: 849–56. DOI: 10.3238/arztebl.2019.0849

► **Supplementary material**

For eReferences please refer to:
www.aerzteblatt-international.de/ref5019

Supplementary material to:

The Role of Local Treatment in Oligometastatic and Oligoprogressive Cancer

by Jan Haussmann, Christiane Matuschek, Edwin Bölke, Klaus Orth, Pirus Ghadjar, and Wilfried Budach

Dtsch Arztebl Int 2019; 116: 849–56. DOI: 10.3238/arztebl.2019.0849

eReferences

- e1. Nordlinger B, Sorbye H, Glimelius B, et al.: Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2013; 14: 1208–15.
- e2. Kemeny MM, Adak S, Gray B, et al.: Combined-modality treatment for resectable metastatic colorectal carcinoma to the liver: surgical resection of hepatic metastases in combination with continuous infusion of chemotherapy—an intergroup study. *J Clin Oncol* 2002; 20: 1499–505.
- e3. Dorn PL, Meriwether A, LeMieux M, Weichselbaum RR, Chmura SJ, Hasan Y: Patterns of distant failure and progression in breast cancer: implications for the treatment of oligometastatic disease. *Int J Radiat Oncol Biol Phys* 2011; 81: S643.
- e4. Friedel G, Pastorino U, Ginsberg RJ, et al.: Results of lung metastasectomy from breast cancer: prognostic criteria on the basis of 467 cases of the International Registry of Lung Metastases. *Eur J Cardiothorac Surg* 2002; 22: 335–44.
- e5. Greenberg PA, Hortobagyi GN, Smith TL, Ziegler LD, Frye DK, Buzdar AU: Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. *J Clin Oncol* 1996; 14: 2197–205.
- e6. Ruiz A, van Hillegersberg R, Siesling S, et al.: Surgical resection versus systemic therapy for breast cancer liver metastases: results of a European case matched comparison. *Eur J Cancer* 2018; 95: 1–10.
- e7. Sadot E, Lee SY, Sofocleous CT, et al.: Hepatic resection or ablation for isolated breast cancer liver metastasis: a case-control study with comparison to medically treated patients. *Ann Surg* 2016; 264: 147–54.
- e8. Chmura SJ, Winter KA, Salama JK, et al.: NRG BR002: a phase IIR/III trial of standard of care therapy with or without stereotactic body radiotherapy (SBRT) and/or surgical ablation for newly oligometastatic breast cancer. *J Clin Oncol* 2016; 34: TPS1098-TPS.
- e9. Cardoso F, Senkus E, Costa A, et al.: 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4) dagger. *Ann Oncol* 2018; 29: 1634–57.
- e10. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Früherkennung, Diagnose, Therapie und Nachsorge des Mammakarzinoms, Version 4.1, 2018 AWMF Registernummer: 032-045OL. www.awmf.org/uploads/tx_szleitenlinien/032-045OL_S3_Mammakarzinom_2019-08.pdf (last accessed on 2 September 2019).
- e11. Chan OSH, Lee VHF, Mok TSK, Mo F, Chang ATY, Yeung RMW: The role of radiotherapy in epidermal growth factor receptor mutation-positive patients with oligoprogression: a matched-cohort analysis. *Clin Oncol (R Coll Radiol)* 2017; 29: 568–75.
- e12. Hu F, Xu J, Zhang B, et al.: Efficacy of local consolidative therapy for oligometastatic lung adenocarcinoma patients harboring epidermal growth factor receptor mutations. *Clin Lung Cancer* 2019; 20: e81–e90.
- e13. Jiang T, Chu Q, Wang H, et al.: EGFR-TKIs plus local therapy demonstrated survival benefit than EGFR-TKIs alone in EGFR-mutant NSCLC patients with oligometastatic or oligoprogressive liver metastases. *Int J Cancer* 2019; 144: 2605–12.
- e14. Xu Q, Zhou F, Liu H, et al.: Consolidative local ablative therapy improves the survival of patients with synchronous oligometastatic NSCLC harboring EGFR activating mutation treated with first-line EGFR-TKIs. *J Thorac Oncol* 2018; 13: 1383–92.
- e15. Elamin YY, Gomez DR, Antonoff MB, et al.: Local consolidation therapy (LCT) after first line tyrosine kinase inhibitor (TKI) for patients with EGFR mutant metastatic non-small-cell lung cancer (NSCLC). *Clin Lung Cancer* 2019; 20: 43–7.
- e16. Gan GN, Weickhardt AJ, Scheier B, et al.: Stereotactic radiation therapy can safely and durably control sites of extra-central nervous system oligoprogressive disease in anaplastic lymphoma kinase-positive lung cancer patients receiving crizotinib. *Int J Radiat Oncol Biol Phys* 2014; 88: 892–8.
- e17. Mehta N, Mauer AM, Hellman S, et al.: Analysis of further disease progression in metastatic non-small cell lung cancer: implications for locoregional treatment. *Int J Oncol* 2004; 25: 1677–83.
- e18. Iacobuzio-Donahue CA, Fu B, Yachida S, et al.: DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. *J Clin Oncol* 2009; 27: 1806–13.
- e19. Planchard D, Popat S, Kerr K, et al.: Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018; 29: iv192–iv237.
- e20. Lodeweges JE, Klinkenberg TJ, Ubbels JF, Groen HJM, Langendijk JA, Widder J: Long-term outcome of surgery or stereotactic radiotherapy for lung oligometastases. *J Thorac Oncol* 2017; 12: 1442–5.
- e21. Widder J, Klinkenberg TJ, Ubbels JF, Wiegman EM, Groen HJ, Langendijk JA: Pulmonary oligometastases: metastasectomy or stereotactic ablative radiotherapy? *Radiother Oncol* 2013; 107: 409–13.
- e22. Chang JY, Senan S, Paul MA, et al.: Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol* 2015; 16: 630–7.
- e23. Barney BM, Markovic SN, Laack NN, et al.: Increased bowel toxicity in patients treated with a vascular endothelial growth factor inhibitor (VEGF) after stereotactic body radiation therapy (SBRT). *Int J Radiat Oncol Biol Phys* 2013; 87: 73–80.
- e24. Barata PC, Mendiratta P, Kotecha R, et al.: Effect of switching systemic treatment after stereotactic radiosurgery for oligoprogressive, metastatic renal cell carcinoma. *Clin Genitourin Cancer* 2018; 16: 413–9.e1.
- e25. Lussier YA, Xing HR, Salama JK, et al.: MicroRNA expression characterizes oligometastasis(es). *PLoS One* 2011; 6: e28650.
- e26. Hanssen A, Riebensahm C, Mohme M, et al.: Frequency of circulating tumor cells (CTC) in patients with brain metastases: implications as a risk assessment marker in oligo-metastatic disease. *Cancers (Basel)* 2018; 10.
- e27. Pitroda SP, Khodarev NN, Huang L, et al.: Integrated molecular subtyping defines a curable oligometastatic state in colorectal liver metastasis. *Nat Commun* 2018; 9: 1793.
- e28. Beckurts KT, Holscher AH, Thorban S, Bollschweiler E, Siewert JR: Significance of lymph node involvement at the hepatic hilum in the resection of colorectal liver metastases. *Br J Surg* 1997; 84: 1081–4.
- e29. Figueras J, Valls C, Rafecas A, Fabregat J, Ramos E, Jaurieta E: Resection rate and effect of postoperative chemotherapy on survival after surgery for colorectal liver metastases. *Br J Surg* 2001; 88: 980–5.
- e30. Arrieta O, Barron F, Maldonado F, et al.: Radical consolidative treatment provides a clinical benefit and long-term survival in patients with synchronous oligometastatic non-small cell lung cancer: a phase II study. *Lung Cancer* 2019; 130: 67–75.
- e31. Collen C, Christian N, Schallier D, et al.: Phase II study of stereotactic body radiotherapy to primary tumor and metastatic locations in oligometastatic non-small-cell lung cancer patients. *Ann Oncol* 2014; 25: 1954–9.
- e32. De Ruysscher D, Wanders R, van Baardwijk A, et al.: 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: 1547–55.
- e33. Endo C, Hasumi T, Matsumura Y, et al.: A prospective study of surgical procedures for patients with oligometastatic non-small cell lung cancer. *Ann Thorac Surg* 2014; 98: 258–64.
- e34. Iyengar P, Kavanagh BD, Wardak Z, et al.: Phase II trial of stereotactic body radiation therapy combined with erlotinib for patients with limited but progressive metastatic non-small-cell lung cancer. *J Clin Oncol* 2014; 32: 3824–30.
- e35. Petty WJ, Urbanic JJ, Ahmed T, et al.: Long-term outcomes of a phase 2 trial of chemotherapy with consolidative radiation therapy for oligometastatic non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2018; 102: 527–35.
- e36. Trovo M, Furlan C, Polesel J, et al.: Radical radiation therapy for oligometastatic breast cancer: results of a prospective phase II trial. *Radiother Oncol* 2018; 126: 177–80.