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Oligometastases: the new paradigm and options for radiotherapy

A critical review

A new paradigm is increasingly determining clinical practice: the oligometastatic state. Radiotherapy plays an important role here, as one of the main therapeutic oncological methods in establishing the new strategic approach for patients with limited metastatic cancer.

Traditionally, patients with cancer are assigned either treatment with a curative intent, in cases where the tumour is localised and there is no indication for metastatic manifestation, or they receive palliative therapy because of lesions that have spread beyond the primary tumour. The general understanding of metastatic disease and especially the mechanisms of the so-called "invasion-metastasis cascade" is currently undergoing fundamental revision [1]. In this context, the perception of metastatic cancer is seen in a more differentiating way with focus on the details of disease manifestations with regard to the number and sites of the lesions. In the future, metastatic cancer is going to be viewed more as a dynamic spectrum than merely as a definite status [2].

For a long time in the previous century, Halsted's doctrine of cancer as a localised and orderly process, which might at some stage start a contiguous spreading into adjacent structures, was predominant. It was challenged by the "systemic theory", assuming a primary systemic state, in most cases involving a complex spectrum of host–tumour interactions, and claiming that local treatment is unlikely to effect the survival of patients [3].

In 1994 Samuel Hellmann [2] stated that cancer is "a heterogeneous disease that can be thought of as a spectrum of proclivities extending from a disease that remains local…" and that "persistent disease, locally or regionally, may give rise to distant metastases and therefore, in contrast to the systemic theory, locoregional therapy is important". In 1995, referring to this *a priori* idea, he proposed the existence of a "clinically significant state of oligometastases" as an interim stage in the natural history of most solid malignancies [4]. Cancer is understood to be an evolutionary process of genesis and especially of progression, which is based on the specific metastatic capacity of each individual tumour. However, basic research results on the biology of metastases need to be linked to clinical data, in order to legitimate current practices. In this review, results from molecular, developmental and cellular biology of metastases are integrated to provide an up-to-date understanding of metastatic capacity of tumours and consequently, to interlace these facts with the clinical discourses of oligometastases. The discussion will start with some questions essential to the understanding of metastases. In a further step, we show relevant clinical implications of the oligometastatic state and corresponding clinical data for lung, liver, bone and brain lesions, limited in number and site, with special respect to radiotherapeutic procedures.

Biology of metastases

Metastases are regarded as the end stage of the patient's life. More than 90% of cancer patients die because of dissemination of lesions in different organs. That is, metastases were found after the treatment of the primary tumour with curative intent; thus, it is a metachronous scenario. They might be synchronously present at initial diagnosis of the primary tumour or in some cases, they are detected previously, without any primary tumour.

Metastasising is a multistep process: a primary tumour that is infiltrating the site of its origin (*invasion*) locally will, at some stage, enter the vasculature of lymphatic and blood systems (*intravasation*). The physical translocation involves the following aspects: circulating tumour cells in blood have to survive many different stress factors, and after finding affinities to a specific tissues (*homing*), they have to exit the bloodstream and enter the parenchyma of the host organ (*extravasation*). The next step is *colonisation*: at the new site, the tumour cells invade the microenvironment, thereby evading the innate immune system, and then they must adapt to the new host and initiate proliferation [1, 5].

An intratumoural *genetic instability* is seen as the basic "condition of possibility" for invasion and metastasising. Some clonal subgroups within a genetically heterogeneous tumour might have a high tendency to metastasise. A higher mu-

tability is seen in those clonal subgroups with an apparently higher rate of metastases [6].

The acquisition of an *aggressive phenotype* is now recognised as a trigger for the metastatic cascade. Genotoxic stress, induced by oncogenes, activation of inhibitory, apoptotic and senescence pathways and telomere attrition, are cell-intrinsic pressures limiting local tumour growth. The evasion of these suppressive streams is a hallmark of the invasiveness of primary tumours [7]. Extrinsic suppressive factors include an extracellular matrix, tensional forces, basement membranes, reactive oxygen radicals, immune response, inhibitory cytokines, regulatory ECM peptides, low pH and, especially, local hypoxia. This last point is a selective component in this context: the cellular response to hypoxia involves the stabilisation of a hypoxia-inducible factor-1 (HIF-1) transcriptional complex, which is an activator of genes that promote angiogenesis, survival, anaerobic metabolism and invasion [8]. Tumours with abundant HIF-1 stabilisation tend to spread metastatically [9, 10].

An important source of the intratumoural heterogeneity is revealed by the fact that tumours are organised hierarchically [11]. The scale of self-renewing *stem cells*, progenitor cells and fully differentiated end-stage cells seems to be present in malignant tumours [12, 13]. The notion of stem cells has changed the understanding of cancer fundamentally [14, 15, 16, 17, 18]. Cancer stem cells are supposed to possess the capability of self-renewal and the generation of heterogeneous lineages of cancer cells within a tumour [19]. Two different theories have been proposed:

- "the stochastic model" claims that every cancer cell within a tumour can ultimately acquire the capacity for self-renewal and multilineage potency, and therefore repopulate an entire tumour [20];
- "the hierarchy model" claim that tumours are heterogeneous and that only a minority of cells serve as stem cells, giving rise to tumours and metastases [1].

Regarding the metastatic capacities of solid tumours, there might be analogies to initiation of the primary tumour and metastases. Both processes depend on the ability of cancer cells to become founder cells that can reproduce unlimited numbers of descendant cells [1].

Additionally, other characteristics may enhance the impact of stem cells on the metastatic capacity of cells: motility, invasiveness and augmented resistance to apoptosis [21]. Developmental biology has defined a *cell-biological programme* that might play a pivotal role in morphogenesis: the *epithelial-to-mesenchymal transition* (EMT). It is an embryologically conserved genetic programme by which epithelial cells downregulate intercellular tight junctions, lose polarity, express mesenchymal markers and manifest an aggressive migratory phenotype [22]. Driven by transcription factors (EMT-TF), the programme may induce mechanisms for activation of nonstem cells into a stem cell-like state and, additionally, to increase the resistance to apoptosis [23, 24]. Motile cancer cells with mesenchymal attributes caused by EMT are attracted to the local vasculature by different factors. Tumour-associated neutrophils contribute to neovascularisation by supplying matrix metalloproteinase-9 (MMP-9). It has been shown that highly disseminating carcinomas recruit increasing levels of infiltrating MMP-9-positive neutrophils and concomitantly exhibit *intravasation* [25]. While in transit, *circulating tumour cells* (CTCs) face many stress factors. They have a relatively large diameter (20–30 µm) that complicates the flow through the tiny capillary system of the lungs, which have a diameter of approximately 8 µm. A large number of circulating cells might be trapped very soon after their release by the primary tumour. However, the lodging process of circulating tumour cells in the capillary bed is the starting point for *homing* onto a new parenchymal environment. A complex network of interactions and distinct adaptive processes are seen to be the basis for colonisation [1].

Specifics of oligometastases

Continuing improvements in morphological and biological imaging and the wide implementation of regular follow-ups are leading to more sensitive and earlier detection of relapse, which enables clinicians to see limited metastases at an early and therefore controllable stage in the trajectory of the diseases.

Proposing an intermediate state of metastases, termed "oligometastases", Hellmann and Weichselbaum [26] stated that in the concept in which the number and site of metastatic tumours is limited, "the evolution of metastatic capacity has intermediate states in which spread may be limited to specific organs and metastases might be present in limited numbers. The clinical implication of this hypothesis is that localised forms of cancer treatment may be effective in patients with oligometastases". In this context, local therapeutic models for oligometastases have been widely investigated and adopted for many cancers.

Generally oligometastases are defined by 1–5 lesions beside the primary tumour. Data has revealed the fact that active intervention in the oligometastatic state might be of measurable clinical benefit for patients [27, 28, 29]. Radiotherapy (RT) could play a determining role in the local control of oligometastatic cancer. Highly conformal radiation therapy in particular, stereotactic ablative radiotherapy (SABR) and brachytherapy may well provide a higher level of therapeutic efficiency and safety compared to minimal or noninvasive methods with lower morbidity, lower costs and the potential for delivering ablative treatments on an outpatient basis. Local control remains the main clinical goal of RT in this scenario, although local control alone does not necessarily reflect the therapeutic potential of RT. In situations of local, locoregional or even systemic progression, RT techniques, such as SABR or brachytherapy, may be repeated in most cases. Most often, ablative doses are delivered to focal liver metastases with the goal of local control and ultimately improving survival [30, 31]. While patients may receive RT for a limited number of metachronous metastases, it has to be discussed whether they are in need of systemic therapy in certain clinical settings. The case of early breast cancer in which single or oligometastases may occur long after the primary therapy in bone or brain in a very limited number and size might exemplify

the rationale for omitting chemotherapy. After application of local RT and its measurable outcome, one could discuss omission of chemotherapy upon provision of image-based confirmation of absence of any other lesion; however, these patients have to undergo short-termed follow-up visits [32]. It is very important to understand potential or hypothesized differences in biological behaviour of those cases with oligometastases within one specified organ and those with oligometastases in two different organs; however no valid data on measurable clinical differences in regard to outcome are available [26]. The large majority of published data are based on local treatment for limited metastases in target organs originating from primary lung, breast and colorectal cancer. These tumours have known patterns of metastatic dissemination, which are described below [26, 27, 28, 29]. Further prospective studies have to discriminate between these two subgroups.

Radiation oncology is experiencing a shift toward more sophisticated high-tech methods, which are redefining the "ballistic" technique in order to deliver higher radiation doses to target volumes, whilst sparing surrounding normal tissues of critical structures by means of

- intensity-modulated radiation therapy, including volumetric modulation arc therapy and similar rotational approaches,
- robotic arm delivery of radiation therapy and
- high linear energy transfer ionising radiation delivery as represented by protons and other hadrons.

Emerging data show that SBRT and brachytherapy in its various treatment models are safe and efficient for local control of limited metastatic lesions. Once the observation of potential efficacy of RT in the oligometastatic state was shown, the question of dose intensity emerged. The respective RT technique (e.g. hypofractionated stereotactic RT, extracranial and intracranial radiosurgery and brachytherapy) might be applied in an appropriate biologic effective dose in order to control the limited local lesion(s). It has to be, at least in regard to intention, a "curative" dose [26, 29, 31, 32].

Clinical experience and challenges are reviewed and discussed below.

Lung metastases

The lungs are one of the common sites of metastasis of solid tumours from different origins. Until now, chemotherapy has been the standard treatment model. Surgical intervention is widely seen as an alternative for a single metastasis, but there are many patients who are not amenable to metastasectomy. For them, minimally invasive techniques such as SBRT are used.

A selection of *prospective* analyses on lung SBRT is shown in **Tab. 1**.

Okunieff et al. [33] treated 50 patients. Each patient had up to five metastases. Thirty of these patients were treated with curative intent with a preferred dose of 50 Gy in 5 fractions (biological equivalent dose [BED] 100 Gy). The local control rate for all lesions at 3 years was 91%, with an overall survival of 25% at 3 years in those treated with curative intent. There was no reported grade 3 toxicity. In their paper Yoon et al. [34] reported on 53 cases. The starting dose was 30 Gy in 3 fractions, which was escalated to 48 Gy in 4 fractions (BED¼105.6). At a median follow-up of 14 months, those treated with 30 Gy in 3 fractions had a local control rate of 70%, those treated with 40 Gy in 4 fractions had a 77% local control rate, and those treated with 48 Gy in 4 fractions had a 100% local control rate. There was no reported grade 3 toxicity. In a multi-institutional phase I–II trial, Rusthoven et al. [30] showed results from 38 patients with a median follow-up of 15.4 months (range 6–48 months). The median gross tumour volume was 4.2 ml (range 0.2–52.3 ml). Actuarial local control at 1 and 2 years after SBRT was 100 and 96%, respectively. Local progression occurred in 1 patient, 13 months after SBRT. Median survival was 19 months. There was no grade 4 toxicity. Most recently, Ricardi et al. [35] reported on 61 patients who were treated with 26 Gy in 1 fraction, 22 who were treated with a dose of 45 Gy in 3 fractions and 3 who were treated with a dose of 36 Gy in 4 fractions. After a median follow-up interval of 20.4 months, local control rates at 2 and 3 years were 89 and 83.5%, overall survival 66.5 and 52.5%,

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Oligometastases: the new paradigm and options for radiotherapy. A critical review

Abstract
Traditional oncology distinguishes between two separate and incommensurable states in the evolution of solid malignancies: the localized disease, which is curable; and the disseminated status, which is per se palliative. Recently, a huge body of evidence suggests a fundamental change in the understanding of cancer, indicating an intermediate state in the trajectory of solid malignancies: the oligometastatic state. The following review will critically analyse existing hypotheses and facts from the basic sciences and try to contextualize it in regard to the clinical evidence available to date. Consecutively, it will try to draw possible clinical consequences for application of radiotherapy in this specific clinical scenario.

Keywords
Oligometastases · Oligometastatic state · Curative options · Radiotherapy · Paradigm shift

Oligometastasen: Neue Paradigmen und Möglichkeiten für die Strahlentherapie. Ein kritischer Überblick

Zusammenfassung
Die traditionelle Onkologie trennt hinsichtlich therapeutischer Optionen zwei grundlegend unterschiedliche klinische Situationen: die lokalisierte Erkrankung mit kurativen Therapiechancen und die disseminierte Situation mit nur noch palliativen Lösungen. Die aktuelle Datenlage suggeriert die Notwendigkeit der Adaptation unseres klinischen Verständnisses onkologischer Erkrankungen im Sinne des Vorliegens einer intermediären, nämlich oligometastasierten Situation. Diese Arbeit setzt sich kritisch mit den Hypothesen und dem Wissen der Grundlagenforschung auseinander und kontextualisiert die vorliegende klinische Evidenz. Ziel ist die Auslotung der Radiotherapieoptionen für oligometastasierte Patienten.

Schlüsselwörter
Oligometastasen · Oligometastasierte Situation · Kurative Therapie · Strahlentherapie · Paradigmenwechsel

Tab. 1 Selected prospective analysis of patients with lung oligometastases treated with radiotherapy

Study	Number, design	Local control	Survival	Dose prescription
Yoon et al. [34]	53, perospective	At 14 months: 70–100%	2 years: 51%	30–48 Gy in 3–4 fractions
Okunieff et al. [33]	50, perospective	3 years: 91%	3 years: 25% for BED 100 Gy	48–57 Gy in 3–10 fractions
Norihisa et al. [50]	34, perospective	2 years: 90%	2 years: 84%	48–60 Gy in 4–5 fractions
Brown et al. [49]	35, perospective	At median 18 months: 71%	At median 18 months: 77%	5–60 Gy in 1–4 fractions
Rusthoven et al. [30]	38, perospective	2 years: 96%	2 years: 39%	60 Gy in 3 fractions
Ricardi et al. [35]	61, perospective	2 years: 89%	2 years: 66.5%	45 Gy in 3 fractions 26 Gy in 1 fraction

BED biological equivalent dose.

Tab. 2 Selected prospective analysis of patients with liver oligometastasised cancer treated with radiotherapy

Study	Number, design	Local control	Survival	Dose prescription
Herfarth et al. [53]	33, prospective	6 month: 75% 12 month: 71%	1 year: 72%	14–26 Gy in 1 fraction
Méndez-Romero [37]	14, prospective	1 year: 100% 2 year: 86%	1 year: 85% 2 year: 62%	12.5 Gy in 3 fractions
Ambrosino et al. [52]	27, prospective	74%	–	25–60 Gy in 3 fractions
Lee et al. [51]	140, prospective	71%		24 Gy in 6 fractions
Rusthoven et al. [38]	47, prospective	1 year: 95% 2 year: 92%	2 year: 30%	12–20 Gy in 3 fractions
Rule et al. [54]	27, prospective	24 month: 50 Gy: 89% 60 Gy: 100%	–	10 Gy in 3–5 fractions 12 Gy in 5 fractions

cancer-specific survival 75.4 and 67% and progression-free survival 32.4 and 22.3%. Toxicity profiles showed just one case of grade 3 toxicity.

Overall, SBRT in this patient group is well tolerated and clinical outcomes in terms of local control and overall survival seem to be achieved with regimes prescribing a BED of 100 Gy. The main endpoint, namely local control, is 89–96% at 2 years. Overall survival, which depends on various factors such as overall dynamics of the disease, performance index and therapeutic regimens pre- and post-RT, is between 39 and 84% at 2 years. Comparison with surgery is impossible due to a lack of randomised trials; the patients treated in the above trials were invariably medically inoperable, which has an impact on overall survival rates. However, the results for SABR are encouraging, and this noninvasive approach is a valid alternative.

Liver metastases

The liver is one of the common sites of metastasis of solid tumours, especially from colorectal cancer. Surgery has proven to be a very effective treatment for limited liver lesions with a 5-year overall survival rate of 40–50% [36]. Chemotherapy has been the additive treatment model. A selection of prospective analyses on liver SBRT is shown in ◘ **Tab. 2**.

In a prospective protocol, Romero et al. [37] achieved a 2-year local control of 86% and 2-year overall survival rates of 62% with SBRT. In another prospective analysis by Rusthoven et al. [38], using 36–60 Gy in 3 fractions, 2-year local control was 92% and a survival rate of 30% was achieved. Fumagalli et al. [39] recently reported on 72 patients with liver metastases who were treated with the Cyberknife technique. The applied dose ranged from 27–54 Gy. The majority received 40 Gy (39%) or 45 Gy (49%), with a dose per fraction of 10 Gy and 15 Gy, respectively. Median treatment time was 8 days with a median follow-up of 17 months (range 14–19 months). Image-guided brachytherapy has been reported as a safe and an effective radiotherapeutic option for the treatment of lesions in liver, lung and other sites. Brachytherapy based on CT-guided insertion of ^{192}iridium high-dose rate sources in the liver with afterloading technique offers a favourable dose distribution within the lesion, including very large tumours >10 cm. Cooling effects by adjacent blood vessels are not a concern in brachytherapy, and the method may be used in lesions close to the liver hilum due to the relatively high radiation tolerance of the bile duct [40]. The application of image-guided brachytherapy seems to be effective in local and regional control of lever lesions. Wieners et al. [41] recently reported on results of a phase II trial. Delivering a median dose of 18.5 Gy (range 12–25 Gy), as a single fraction, in 41 consecutive patients with 115 unresectable hepatic metastases in breast cancer with a median follow-up of 18 months, local control after 6, 12 and 18 months was 97, 93.5 and 93.5%. Intra- and extrahepatic progression-free survival was 53, 40 and 27%, and overall survival was 97, 79 and 60%, respectively.

No dose dependency of local tumour control was observed if a minimal dose of 15 Gy was applied. However, in case of local recurrence, due to the relative independence of brachytherapy to the size of the tumour volume treated and the low impact on liver function, CT-guided brachytherapy could be repeated [40, 41].

Overall, SBRT for patients with liver lesion is feasible.

The main endpoint, namely local control, is 71–100% at 2 years. Due to highly complex scenarios in the trajectory of the disease and continuing changes in the regimens of chemotherapy and biologicals, the role of overall survival has to be re-evaluated permanently according to the current standards.

Brain metastases

The optimal conservative treatment for patients with oligometastases of the brain is still controversially discussed [42].

Tab. 3 Selected prospective analysis of patients with spin oligometastases treated with radiotherapy

Study	Number, design	Local control	Survival	Dose prescription
Nguyen et al. [47]	48, prospective	12 months: 82.1%	–	24 Gy in 1 fraction, 27 Gy in 3 fractions, 30 Gy in 5 fractions
Tsai et al. [57]	69, prospective	10 months: 96.8%	–	15.5 Gy in 2 fractions
Yamada et al. [58]	93, prospective	15 months: 90%	–	24 Gy in 1 fraction
Gibbs et al. [59]	76, prospective	84% (clinical data)	–	16–25 Gy in 1–5 fractions
Ryu et al. [60]	49, prospective	78%		8 Gy in 1 fraction as boost

There is a broad spectrum of techniques and concepts available, including whole brain radiotherapy (WBRT) alone, whole brain plus stereotactic radiosurgery (SRS) boost and stereotactic radiosurgery alone. Survival advantages of SRS have been reported by randomised trials [43]. In a group of 132 patients with 1–4 brain metastases, randomly assigned to receive WBRT plus SRS or SRS alone, Aoyama et al. [44] reported no significant difference in survival (8 months versus 7.5 months) and 1-year local control (72.5% versus 88.7%). Although SRS alone was associated with increased intracranial progression as compared with WBRT plus SRS, no differences in the frequency of neurological deaths and preservation of neurological function were observed. Similarly, the recent EORTC 22952-26001 study on the adjuvant WBRT versus observation after SRS or surgical resection of 1–3 cerebral metastases showed that adjuvant WBRT was able to reduce the frequency of intracranial progression but failed to improve the median survival [45].

Spinal metastases

Stereotactic radiotherapy is a clinically proven option as primary and postoperative treatment, and as retreatment for previously irradiated patients, with good results on pain control, neurological symptom release and quality of life, although lack of prospective data, especially randomised data, makes it difficult to reach conclusions. The heterogeneity of clinical scenarios is frequently the cause for differences in therapeutic concepts using RT with or without systemic drugs [46]. A selection of papers on spinal lesions SBRT is shown in **Tab. 3**.

Nguyen et al. [47] recently reported on results of SBRT in 48 cases. Patients received either 24 Gy in a single fraction, 27 Gy in 3 fractions, or 30 Gy delivered in 5 fractions. After a median follow-up time of 13.1 months (range 3.3–54.5 months), the actuarial 1-year spine tumour progression-free survival was 82.1%. At the pretreatment baseline, 23% patients were pain free; at 1 month and 12 months post-SBRT, 44 and 52% patients were pain free, respectively. No grade 3–4 neurological toxicity was observed. Gerszten et al. [48] published results on a cohort of 500 patients with spinal metastases who underwent radiosurgery. The prescribed dose ranged from 12.5–25 Gy (mean 20 Gy). Tumour volume ranged from 0.20–264 ml (mean 46 ml). Long-term pain improvement was achieved in 290 of 336 cases (86%). Long-term tumour control was demonstrated in 90% of lesions treated with radiosurgery as a primary treatment model and in 88% of lesions treated for radiographic tumour progression. Twenty-seven of 32 cases (84%) with a progressive neurological deficit before treatment experienced at least some clinical improvement.

Local radiotherapeutic treatment is evidently effective and can be safely applied for spinal lesions.

Bone metastases

Oligometastases of bone have been reported in prostate and breast cancer. Overall high-dose radiotherapy provides long-term relief of pain and can even improve overall survival. In 2009 Milano et al. [32] reported on 85 metastatic lesions in 40 breast cancer patients treated with SBRT, achieving a 2-year overall survival rate of 76% and a 4-year overall survival of 59%. Among these, the most favourable prognostic factor for breast oligometastatic patients was metastases only involving bone. This indicated high-dose radiotherapy using SBRT for bone metastases could contribute to patient survival.

Conclusion

The role of radiation therapy for the treatment of metastatic cancer has evolved enormously in the last decade. Thanks to emerging technologies, especially stereotactic radiosurgery, image-guided RT or variations of intensity-modulated RT, radiation oncology is gaining popularity as an effective and safe model in all stages of cancer. Thus, the oligometastatic state that is assumed to be a different phase in the evolution of neoplastic disease, being limited in terms of number and site of metastatic lesions, seems to be an appropriate application field for emerging RT technologies to prove the principle. While some crucial issues are still under discussion—selection of patients, timing, dose regimen, radiobiological consideration and prognosis—more clinicoconceptual questions need to be asked:

- **What is the difference in biologic behaviour between synchronous and metachronous lesions?**
- **How to use available imaging technologies for definition of the oligometastatic state?**
- **What would be the effective and safe combination with systemic therapeutics like biologicals or conventional chemotherapy?**
- **Where is the frontier line between palliative and "semicurative" intention and goals in this context?**

These unanswered questions need to be analysed by prospective and more focused and targeted study designs in order to locate and position radiation therapy as a leading method of treatment of oligometastases.

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