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Metastases-directed local therapies (MDT) beyond genuine oligometastatic disease (OMD): Indications, endpoints and the role of imaging

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ABSTRACT

To further personalise treatment in metastatic cancer, the indications for metastases-directed local therapy (MDT) and the biology of oligometastatic disease (OMD) should be kept conceptually apart. Both need to be vigorously investigated. Tumour growth dynamics – growth rate combined with metastatic seeding efficiency – is the single most important biological feature determining the likelihood of success of MDT in an individual patient, which might even be beneficial in slowly developing polymetastatic disease. This can be reasonably well assessed using appropriate clinical imaging. In the context of considering appropriate indications for MDT, detecting metastases at the edge of image resolution should therefore suggest postponing MDT. While three to five lesions are typically used to define OMD, it could be argued that countability throughout the course of metastatic disease, rather than a specific maximum number of lesions, could serve as a better parameter for guiding MDT. Here we argue that the unit of MDT as a treatment option in metastatic cancer might best be defined not as a single procedure at a single point in time, but as a series of treatments that can be delivered in a single or multiple sessions to different lesions over time. Newly emerging lesions that remain amenable to MDT without triggering the start of a new systemic treatment, a change in systemic therapy, or initiation of best supportive care, would thus not constitute a failure of MDT. This would have implications for defining endpoints in clinical trials and registries: Rather than with any disease progression, failure of MDT would only be declared when there is progression to polymetastatic disease, which then precludes further options for MDT.

Introduction

Considerable progress in the treatment of limited metastatic disease in solid malignancies is witnessed. Prospective studies in appropriately selected patients not only suggest excellent local control of treated lesions, but amelioration of progression-free survival using metastases-directed local therapy (MDT) in patients with limited metastases [1–7]. MDT denotes a local treatment that is used to lead to complete ablation in the sense of removal of the potential to grow, of targeted lesions. This can either be accomplished by physical removal of lesions through excision, or by transforming their tissue so that they lose their potential to grow. MDT thus comprises stereotactic ablative radiotherapy (SABR), radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, metastasectomy, or other comparable modalities.

Two phase II clinical trials investigating local consolidative radiotherapy in limited metastatic cancer [4,6,7] – although less than ablative doses had been prescribed in one study [4] – were closed prematurely by data safety monitoring boards, because local treatment yielded a positive effect precluding continued randomisation of patients to the control arm. Both trials are prominently published and increased the level of evidence concerning local treatment of metastases, although definitive studies powered to demonstrate superiority of MDT in defined oligometastatic situations are still underway. Active phase II/III trials are listed in Jasper et al [8].

Much remains to be investigated, and we will discuss below some aspects that might influence both study design and clinical decision-making in the use of MDT for individual patients. Especially, the accuracy of indications for MDT in metastatic disease of limited extent needs to be improved as to offer the treatment to all patients who might benefit, while sparing those for whom it would likely be futile and thus only contribute unnecessary procedures with potential risks and toxicities [9].

Coining the term oligometastatic disease (OMD) in 1995 has markedly boosted considerations regarding MDT and has aroused the

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attention of radiation oncologists in particular [10–15]. However, MDT using surgery preceded the OMD discussion [16,17]. The OMD discussion, in turn, was paralleled by a dramatic emergence of the possibilities of stereotactic ablative treatment for intra- and extracranial metastatic lesions with ionising radiation due to progress in treatment planning and -delivery technology [14]. Here, we will argue that a reasonably considered treatment intention, based on an adequately described clinical situation and history in an individual patient, rather than narrowly defined OMD should guide the delivery of MDT. There is lacking precision and guidance regarding indications for MDT. To fill these knowledge gaps regarding indications and optimal delivery of MDT, it is important to include as many patients as reasonably possible in clinical trials and prospective registries investigating local treatment of metastases.

Any neoplastic growth is biologically determined. Biological characteristics – discovered or still to be discovered – determine growth rate and patterns of growth and spread. However, clinical growth rate and patterns of spread may be observable in the absence of molecular genetic characterisation. Clinical imaging, especially dynamic imaging over time (weeks, months, years) typically reveals individual, precise, and personalised data about the neoplastic disease of a given patient [18,19]. Metastasis-doubling time of any given metastasis and pattern of metastatic spread is measurable when appropriate imaging modalities are used [20,21]. It yields highly individualised information about the biology and course of disease in given patients.

The main purpose of this paper is to argue.

(1) for keeping concepts of OMD and MDT apart,
(2) for replacing the criterion of a certain numerical upper limit of metastases (usually three or five) with the countability of lesions over the entire course of metastatic disease, and
(3) to separate the technical endpoint of local recurrence of treated metastatic lesions from the oncological endpoint: the appearance of uncountable metastases, which would constitute oncological failure of an MDT approach.

We will argue that these issues are rooted in the tumour biology of metastatic cancer, which in turn can be clinically assessed by serial imaging.

Indication

Recommending and administering any medical treatment requires an indication. An indication is a defined medical situation constituting a valid reason to use a particular treatment. It can be relatively simple or highly complex. A simple indication would be, e.g., proof of presence of a specific germ in a seriously ill patient yielding a valid reason to administer an antibiotic known to be active against the germ. In contrast, the indication for MDT for metastatic disease typically is an instance of a complex indication, partly because disease having systemically spread suggests being at odds with a local treatment approach per se. Only special side-constraints may render such treatment reasonable.

In complex oncological situations, where the question at stake is a tailored indication for a given patient, it is challenging and often unrealistic to test every potential scenario in a prospective randomised trial, undoubtedly the golden standard to assess the effectiveness of a new drug. An oncological situation that is complex in terms of patient-, treatment-, disease-, and comorbidity-factors requires tailoring a treatment strategy using available elements of treatments. Registries prospectively collecting quality-controlled data as potentially relevant factors might constitute the optimal methodology to advance knowledge in such situations [22]. Based on these data, predictive decision-support models need to be developed, that have to be validated and eventually to be adapted in independent cohorts.

A medical situation forming an indication to use local treatment aiming at complete removal of a clearly identified metastatic lesion must fulfil several criteria, if it is to constitute a valid reason for such treatment. The following classes of factors are minimally involved in forming an indication for MDT [23].

(1) The metastatic lesion must be clearly demarcated, or in other words, metastases that can be considered for local treatment need to be countable. Any unclear suspicious lesions form a serious challenge at least, for the reasonability of MDT, because such lesions suggest the presence of actively growing microscopic disease forming an iceberg of disease. Taking away the tip of an iceberg with MDT would not remove the iceberg.
(2) A number of disease characteristics form a class of candidate factors in an indication for MDT of metastases: histology, molecular, genetic traits (e.g., mutations, deletions, rearrangements); stage of the disease: size, extent, invasion in and destruction of parts of organs. Typically, these factors are assessed by taking biopsies, imaging or, if resection is part of the treatment, by an appropriate workup of resection specimens.
(3) Next, previous and concomitant treatments, especially treatment given for metastatic disease of the index neoplasia is an important factor affecting reasoning about MDT for metastases. Both prior local and systemic therapies of all kinds play a role, and their actual or reasonably assumed effectiveness (response) in a given patient confer reasons for or against using MDT in the course of metastatic disease.
(4) Patient characteristics such as age, general condition, or comorbidities, form another class of factors contributing to an indication for MDT of metastases. These are the least specific factors as they play a role for any therapeutic option in neoplastic diseases at any stage.

All these factors mentioned above are usually derived from inclusion criteria of clinical trials upon which the indication of a certain treatment in question is based. Therefore, these characteristics are generally unproven as such, as inclusion criteria in trials form the background of clinical investigation without being subject to inquiry themselves. Tested treatments are simply not proven in cohorts excluded from clinical trials, and this is only a logical consequence: there is no evidence for the efficacy of a treatment in question in patients who belong to a cohort that was excluded from trial participation.

Treatment history as a relevant factor for any treatment in the metastatic stage is again typically derived from decisive clinical trials. Treatment X may be indicated in a certain line, e.g., after failure of platinum-based chemotherapy or, if surgical resection is deemed too risky. Here again, the definition of the indication for treatment X is derived from inclusion criteria of clinical trials, where treatment X proved to be effective for included patients. Of note, any inclusion criteria constitute an educated and more or less well-informed statement, but they are not proven by the clinical trial themselves. Frequently, they at least partly depend on clinical realities such as the prospect to include enough patients in order to get the study done in a reasonable amount of time, which is in conflict with the need to limit participation to avoid diluting any effects of the treatments tested.

Of note, although inclusion criteria can never be tested themselves in clinical trials, but are assumed, they still define the extent of any resulting indications of treatments that turned out beneficial in clinical trials. Therefore, clinical trials are of limited value to prove factors of treatment indications in any scientifically strict sense. Subgroup analyses that would approach this question are typically just one source for hypotheses, among other hypothesis-generating investigations such as modelling studies from prospectively collected data [24].

Metastases-directed local therapy is not limited to genuine oligometastatic disease

Is local treatment of metastatic cancer (M1) ever reasonable? It depends on a range of conditions forming a complex indication, and it likely is most reasonable for limited M1.

Here, we will argue that OMD is just a special case forming a reasonable indication for MDT in M1-disease: There may be situations, where MDT in M1 may be a reasonable treatment, well beyond OMD in the strict sense. Thus, how is it possible to define limiting conditions in which MDT should be considered from a clinical perspective?

In case of a relatively long expected survival, removable symptoms may require permanent ablation of metastases for the rest of the patient's life. E.g., brain metastases, obstruction, or spinal cord compression typically require treatment that offers the best chance of permanent resolution of resulting symptoms, regardless of whether they occur at an oligo- or polymetastatic stage of disease.

For asymptomatic metastases, MDT should be considered in several scenarios: when cure seems realistically possible; to permanently prevent symptoms; to prolong life without treatment burden (i.e. to postpone or avoid more burdensome treatment modalities with repeated hospital visits and procedures); or to prolong life with no or minimal treatment toxicities.

A characterisation of the types of OMD for which MDT such as SABR could be considered was elaborated in a recent Delphi-based endeavour towards classification of OMD [22]. In this comprehensive classification system it is seen that the term OMD has already been widened to include a partly oligometastatic appearance of polymetastatic disease. Ablation of the oligometastatic component of metastatic disease is widely believed to be oncologically beneficial even though these patients do have polymetastatic disease. From this characterisation it follows that true OMD is only a special case of MDT and not an absolute requirement. Technical feasibility of different modalities of MDT and their potential clinical usefulness, taking into account the individual situation of a given patient, rather than the molecular basis of OMD will probably govern treatment algorithms for MDT in the near future. A decision tree with five main nods has been proposed by experts [22]:

(1) Genuine OMD versus therapy-induced OMD that had been polymetastatic before should be distinguished: metastatic propensity is different, i.e., low/high. Even in therapy-induced OMD there are patients with various primary tumours with long and often indolent courses of disease, where MDT is likely to contribute to prolonging asymptomatic lifetime, but is unlikely to cure the disease.
(2) De novo versus repeat OMD: when OMD recurs as metastatic disease with very few lesions that are again amenable to MDT, the question arises whether repeating MDT without starting systemic therapy comprises one or two treatment series (see below, this paper).
(3) Synchronous versus metachronous OMD: it is quite clear that detection of metastases earlier rather than later intuitively indicates more aggressive disease. However, if one or two removable and not too small lesions are present at primary tumour presentation, this may suggest better prospect than detection of two small metastatic lesions nine months post treatment of the primary. Thus, synchronous and metachronous OMD might need further refinement regarding definition of optimal indications and timings of MDT.
(4) In the course of the disease: Is the patient under active systemic treatment when OMD is stated? If so, MDT is used as an adjuvant treatment to active systemic therapy that has obviously been rather effective so that it induced OMD. Thus, persistent or progressive lesions may be addressed by MDT, which aims to ablate clones that are resistant to the systemic agent: That same systemic agent would in turn be continued to maintain the beneficial deep response it had achieved in other lesions. If OMD is detected at a time when active systemic treatment is not administered, such oligorecurrence could also be addressed using MDT rather than initiating another (or even the same) systemic treatment that had already had a beneficial effect for some time. Likely, there is a wide range of interactions between local and systemic agents in induced OMD as well as in oligorecurrence that will require quite a few studies in the future.
(5) In repeat OMD, metastases might show oligoprogression or oligopersistence: a gradually more shallow response to systemic therapy could lead to the appearance of new lesions or persistence of some lesions. Oligopersistence seems to be the biologically least favourable OMD-state as it suggests only partial response to systemic treatment for some lesions. It could, however, also be the other way around: progression of one or a few lesions on systemic therapy could indicate less favourable biology [25].

Indications can be made in all categories of OMD, but at higher or lesser percentage of affected patients, and with purportedly varying magnitudes of benefit of MDT [25–27]. Seemingly, the factor of systemic treatment in addition to MDT – preceding MDT or following MDT – is a crucial variable factor helping to classify OMD. The motivation for administering MDT in most, if not all, of the clinical scenarios outlined above stems from the assumed underlying biology of the individual patient's presenting metastatic disease, which can be assessed by clinical imaging.

Biological basis of indications for metastases-directed local therapy

Consideration of the biological framework of malignant growth dynamics [28,29] is probably the most important issue related to local treatment of metastatic cancer. Clinical imaging plays a crucial role in making tumour biology tangible by making disease progression more predictable in an individual patient.

The dynamics of metastasis formation reflects complex biological mechanisms known as invasion-metastasis cascade [30]. Given the highly multifactorial nature of metastatic growth, it seems unlikely that actionable biological parameters that significantly support administration or withholding of MDT in clinical practice will become available in the very near future [31–34]. Ideal biological parameters would be blood-borne, given the sometimes difficult accessibility of metastases for biopsy. In contrast, clinical imaging is rapidly advancing including multiparametric data acquisition and can readily be employed for making MDT indications [18–21].

It takes about 21 to 29 tumour-doubling times (TDT) from a single cell to a just imageable metastasis, with TDT typically ranging between 2 and 3 months in most solid cancers [28,29]. In other words, it takes some four to seven years from a single-cell stage to a macroscopic lesion of just less than one centimetre. Timing is therefore key: any detected or detectable metastasis has originated a long time before detection. Thus, based on two measurements of the diameter of target lesions in the past, a simple spreadsheet calculation allows predicting lesion dimensions at future time-points (of course, measuring-uncertainty needs to be taken into account).

It is therefore unlikely to miss the window of opportunity to local treatment of a metastasis, if one or two TDTs are allowed to pass with the idea to attain a clearer picture about the pattern of spread. In particular, to get an idea whether multiple lesions will pass the detectability horizon within weeks or a few months. At least theoretically, starting MDT at a later point in time in those patients who do not develop additional measurable lesions within 3 to 6 months might be even more appropriate. It would spare patients about to enter polymetastatic disease likely futile MDT.

Metastasis-to-metastasis spread has been found in post-mortem

analyses, but typically it occurs late in the course of disease [35,36]. It would entail a risk for patients, if it happened early in limited metastatic disease and from a metastasis with relatively low volume. However, even if a metastasis would spread a new metastasis, this would still only lead to a macroscopic lesion four to seven years later for reasons of biological growth dynamics mentioned above. Testing this scenario in clinical trials seems thus virtually impossible.

Appropriately selecting patients for MDT is highly important without question [29]. Primary histology, disease-free interval and number of metastases have been used to define appropriateness for MDT of metastatic lesions in most studies. Disease-free interval is a function of histology and metastatic growth rate, while the number of metastases relates to pattern of spread as it implies many or just very few clones having survived colonisation of the organism. In addition, this hints towards tumour-host interactions (tumour micro-environment), generally involving the immune system in a broad sense [30].

Girard et al rightly point out that size and distribution of size of metastatic lesions has not been given sufficient emphasis in the context of management of OMD [29]. In particular, the absence of very small lesions (order of magnitude, a few millimetres on CT-imaging) that might be suspicious for metastases increases the chance of a reasonably long interval without new lesions appearing in the near future. The tumour growth rate is the reason for this conclusion, as such lesions have grown for an average of 56 to 87 months, i.e. five to seven years [28]. When they become detectable on CT, they are therefore not biologically new at all.

In conclusion, any imaging-derived signs of metastatic disease, where benefit from MDT seems likely, are a function of tumour doubling time or growth rate of metastatic lesions, combined with low metastasis-seeding efficiency of eventually circulating tumour cells. These biological features of cancers can be derived from proper use and interpretation of high-resolution CT, MRI, and PET-imaging.

Countability rather than number of metastases and clinical imaging

The recommendation of an MDT is indeed – and at the same time should be – a function of the clinical scenario, going beyond the number of metastases and beyond oligo-/polymetastases. Rather, the countability of the metastatic lesions plays an important role here.

Take a patient with NSCLC cT1N1 with one symptomatic brain metastasis on high-resolution MRI plus multiple small lung lesions that are highly suspicious for metastases: This patient has polymetastatic disease and still has a clear and long established indication for MDT of the brain metastasis, be it surgery or radiosurgery. Similar scenarios are possible where MDT may be indicated, or at least, considered. The borderlines up to which MDT could be useful are blurred, and moving. In addition to tumour growth dynamics, they depend on systemic treatment options for given tumours.

Oligorecurrent, oligoprogressive, and oligopersistent disease could be just gradually different regarding response to systemic treatment or else they might be biologically different diseases. From a treatment perspective, they are certainly only gradually different and, for the time being, MDT could be recommended in either scenarios. Indications will typically have to rely on results from imaging studies. In an attempt to refine indications for MDT, taking into account four points might accelerate progress:

(1) Patients should be included in prospective studies and registries with as complete as possible follow-up information regarding disease progression, including further therapies and survival.
(2) Previous treatments of primary tumours and metastases including time-stamps need to be recorded as this comprises most essential information regarding the biology of disease in an individual patient.
(3) It seems to be reasonable to view repeat-MDT as one treatment series, even if different local ablative modalities might be involved, as it is frequently possible to repeat MDT for more than one lesion. After all, the treatment type is the same as long as it is designed to radically eliminate countable (i.e., macroscopic) metastases.
(4) MDT should be driven by comprehensive imaging in order to properly assess countability of metastases and to gain information about suspicion of additional metastatic lesions at the edge of detectability, as this might contain critically relevant information regarding appropriateness or inappropriateness of MDT. The type of imaging that should be chosen mainly depends on the location of involved organs.

Given the wide range of clinical presentations, it is clear that the spectrum of metastatic disease is highly diverse and there is a continuum of probability concerning the effectiveness of MDT. Theoretically, lesions that are demarcated and can be counted can be targeted by local treatment approaches aiming at their complete removal. The number of lesions, especially when paying attention to the course of metastatic disease, is less important in this respect. In the currently recruiting SABR-COMET-10 clinical trial [37] and the EORTC-ESTRO OligoCare prospective observational study [22] the number of lesions is four to ten and undetermined, respectively. Countability is a time-independent criterion in addition. This means that new metastases can appear repeatedly over time, given that they are countable, non-diffuse, and demarcated. In such cases, repeat-MDT may be appropriate. Information from the OligoCare cohort about current practice patterns about the number of lesions treated with MDT is forthcoming.

Failure of local treatment of metastases and the unit of MDT

It is challenging to consider the question of what should be regarded as the unit of MDT, which is closely linked with the question of what should be regarded as failure of MDT. It is often technically possible to administer MDT at one point in time (e.g., comprising three lesions at one treatment episode) or alternatively, in more than one sessions. Additionally, there are clinical situations where two metastatic lesions are best ablated using two different treatment modalities such as SABR for one, and surgery for the other lesion. If there are two lung metastases of 15 mm each, one sitting quite centrally in the right upper lobe, the other very peripherally in the costo-phrenic recessus in the left lower lobe, the patient could be best off with a bimodal treatment strategy. To avoid lobectomy, the first lesion could be ablated using SABR, the other lesion could be removed by wedge-resection or segmentectomy using video-assisted thoracic surgery (VATS) to avoid large safety margins at SABR – or even geographic miss – due to respiratory tumour motion, therewith optimising lung-function-sparing treatment. This way the patient would be treated with minimal toxicity and risk. Should this treatment be counted as one treatment episode as if both lesions were treated with SABR in one treatment session? From an oncological perspective, quite probably, yes.

Furthermore, if one new lesion appears months after ablation of the first lesion, which can again be subjected to MDT: should this be regarded as progression of disease requiring salvage or next line of treatment, or should it be called another cycle of one and the same line of MDT? The treatment unit might thus rather be locally ablative interventions to any clearly countable metastases, which could happen in one single or in several sessions, where any additional lesions would elicit additional sessions of MDT, as long as the disease has not progressed to a widespread stage. The number of lesions accumulating over time might become higher than three or five, the most frequently used, but admittedly arbitrary, numerical limit of OMD. Widespread progression would constitute failure of an MDT-strategy (failure of local strategy, FLS) and consecutively result in change of the line of therapy to systemic agents or even best supportive care (Fig. 1). A special case here

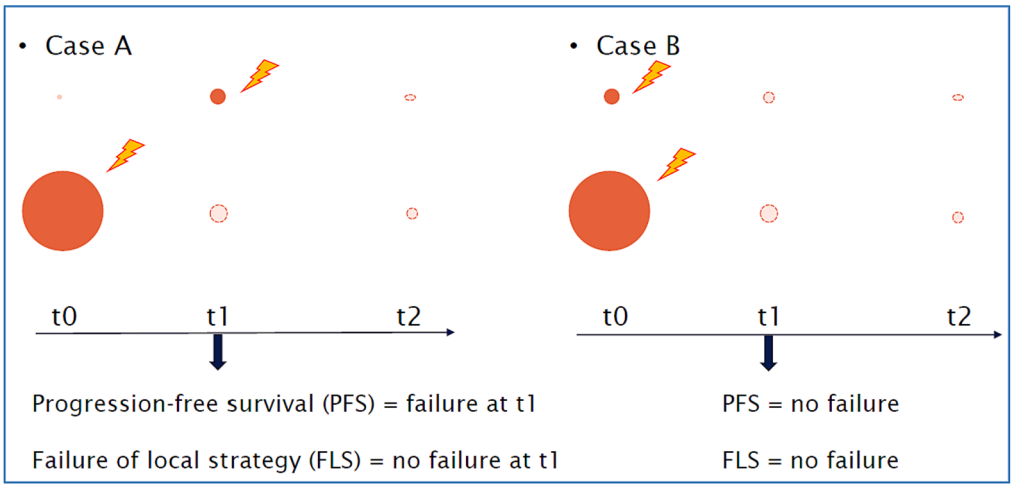

Fig. 1. In case A, two metastatic lesions receive MDT at two different time-points. One would have to declare treatment failure at time-point t1, if the classical endpoint PFS were used, in contrast to using FLS, were the situation in case A would not be declared a failure. Case B is hardly oncologically different from A, and at t2, A and B might exhibit the same result.

would be local recurrence of a locally treated metastasis, that can be locally salvaged using MDT again (e.g., salvage surgery for local failure of SABR; salvage SABR for local failure of resection). Also, radiofrequency ablation typically can be repeated for locally incomplete ablation [38]. From an oncological perspective, even local recurrence of a treated metastasis that is again amenable for MDT (same or different modality), might not have to be regarded as failure of an MDT-approach (FLS). However, from a technical rather than from an oncological perspective, local progression of a treated lesion has to be seen as failure of that treatment. For comparisons between two different modalities of MDT, local progression of treated lesions is therefore a valid endpoint [39–41].

In systemic treatments given for metastatic disease, failure of an agent usually implies progression while the agent is still being administered [42]. Implicitly, all lesions, visible or not, are treated due to the systemic route of administration of the agent. Therefore, progression under treatment means progression of lesions that have already been exposed to the agent and obviously have acquired resistance against the substance. Recently, settings emerge where patients with polymetastatic disease, who are given a certain systemic therapy that had led to response for some time, are suffering progression of only very few, frequently one or two, lesions. In this oligoprogression situation, MDT is sometimes considered to ablate the lesions that had evaded the systemic treatment in order to justify continuation of that very systemic treatment beyond formal progression, as long as that progression is reverted by MDT [22].

This would have consequences for endpoints in studies as failure of MDT would be declared in case of progression beyond amenability of metastases for MDT [43]. It appears to be the oncologically most straightforward approach to decide about success or failure of MDT in given clinical scenarios (Fig. 1). In addition, the actual time on metastases-directed treatment could be used as a parameter of efficiency (benefit/expenses) of such treatment, be it systemic or local.

Such an approach could even work in a setting where systemic therapy and MDT are administered in parallel, with MDT given for either oligopersistence or oligoprogression of a few countable metastatic lesions, where again disease that has spread diffusely would designate failure of the current treatment line – systemic agent plus MDT – and trigger a switch of the therapeutic regimen. Here, switching to a new drug regimen or to supportive care would be the leading component of the therapeutic approach and would designate failure of both MDT and the systemic agent.

Conclusions

A few summarising conclusions can be drawn by considering the classification of OMD, the question of indication for MDT, and how clinical imaging may visualise tumour biology. First, OMD appears to be a special case for MDT: MDT is not limited to genuine OMD, but there are good reasons for MDT of limited metastatic disease beyond OMD. Even if OMD might once be biologically defined on a cellular level, indications for MDT will likely not become refined to OMD, since OMD is not a necessary condition for a proper indication for MDT as discussed in this paper. To advance the field, MDT should always be used with an explicitly formulated treatment intention, clearly describing the intended aim of treatment, together with a clear description of the status quo as well as disease and treatment history. Clinical serial imaging plays a crucial part in this. Derived from the growth dynamics of metastases, it is suggested that the unit of MDT should include repeated sessions for newly emerging lesions. Failure of an MDT-approach for metastatic disease should be concluded at systemic progression to uncountable metastases, which implies infeasibility of complete ablation of all metastases.

Treatment aims of MDT are multiple and there do not seem to be good reasons to exclude any of them:

(1) Prolonged progression-free survival and preventing or postponing symptomatic metastases
(2) Prolonged progression-free survival and prolonging a treatment-free interval
(3) Continuation of effective and life-prolonging systemic treatment when part of the lesions respond or are controlled while a few lesions progress (and are ablated by MDT).
(4) Prolonged overall survival, even if freedom from disease is not realistically achievable
(5) Prolonged freedom from disease, which clinically comes down to freedom from detectable disease
(6) Cure in cases with very few visible metastases in tumours that have seeded a very limited number of metastases in the absence of any subclinical or dormant disease

MDT should be developed independently of the OMD-debate regarding its indications and clinical reasonability. Separating the question of biologically defining oligometastatic disease as a separate stage of disease, or a class of tumours exhibiting characteristic pathways of proliferation, from the clinical question of how to address the disease

of patients with limited numbers of distant metastases might help to advance both fields. Clearly, there will continue to be overlaps between genuine OMD and indications for MDT, but overlaps will remain incomplete.

The cornerstone of MDT as an integral part of the treatment of metastatic disease should be clear clinical criteria: Metastatic lesions are clearly demarcated on high-resolution imaging and countable in the single-digit range. The technical feasibility of complete ablation of all lesions remains critical [44]. Either all lesions are completely resectable or they can be treated with ablative doses of the effective agent (ionising radiation in SABR, heat in RFA or MWA, or cold in cryoablation), or combinations of these modalities are required to optimise the risk–benefit ratio due to technical peculiarities of the modalities employed.

Author contributions

Joachim Widder, conception, writing of draft, intellectual input, revisions, approval of final manuscript. Inga-Malin Simek, intellectual input, revisions, approval of final manuscript, Gregor M. Goldner, intellectual input, revisions, approval of final manuscript, Gerd Heilemann, intellectual input, revisions, approval of final manuscript, Jan F. Ubbels, intellectual input, in-depth discussions, revisions, approval of final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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