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Does Radiotherapy Have Curative Potential in Metastatic Patients? The Concept of Local Therapy in Oligometastatic Breast Cancer

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Keywords
Breast cancer · Oligometastases · Radiotherapy · Stereotactic body radiotherapy, SBRT

Summary
In 1995, Hellmann and Weichselbaum defined for the first time the term oligometastases which is used to describe limited metastasis with a maximum of 3–4 clinically detectable metastases. It is assumed that these patients have a better prognosis and that local treatment of the metastases plays a significant part in the further development of the disease. Therefore, these patients could benefit from a curative local therapy of the manifested metastases. Local therapy measures include mainly radiotherapeutic methods alongside invasive ablative processes, such as surgical resection and radiofrequency ablation. Patients subjected to radiation therapy benefit especially from the usage of modern precision technology as it reduces the radiation exposure to the normal tissue, and because short radiation sessions with escalating doses are possible (e.g. radiation surgery, image-assisted radiation therapy, stereotactic radiation). Initial clinical studies show very good local tumor control rates which are on a par with resection and ablative methods, but with very few side effects and risks. This article summarizes the integration of the concept of oligometastases in the radiotherapy of limited metastatic breast cancer.

Schlüsselwörter
Mammakarzinom · Oligometastasierung · Radiotherapie · Stereotactic Body Radiotherapy, SBRT

Zusammenfassung
Unter dem von Hellmann und Weichselbaum 1995 erstmals verwendeten Begriff der Oligometastasierung versteht man eine limitierte Metastasierung mit maximal 3–4 klinisch detektierbaren Metastasen. Es wird vermutet, dass diese Patienten eine bessere Prognose haben und dass die lokale Kontrolle der Metastasen für den weiteren Krankheitsverlauf eine Rolle spielt. Diese Patienten könnten daher von einer kurativen lokalen Therapie der manifesten Metastasen profitieren. Als lokale Therapiemaßnahme steht neben der Resektion und invasiven ablativen Verfahren (z.B. Radiofrequenzablation) auch die Radiotherapie zur Verfügung. Bei der Strahlentherapie von Metastasen profitieren Patienten in besonderem Maße vom Einsatz moderner Präzisionstechniken, weil dadurch die Strahlenbelastung des Normalgewebes reduziert wird und Kurzzeitbestrahlungen mit Dosiseskalationen möglich sind (z.B. Strahlenchirurgie, bildgeführte Strahlentherapie, stereotaktische Bestrahlung). Erste klinische Studien zeigen sehr gute lokale Tumorkontrollraten, die der Resektion und den ablativen Verfahren gleichwertig sind, aber sehr wenig Nebenwirkungen und Risiken beinhalten. Der vorliegende Artikel fasst die Integration des Konzeptes der Oligometastasierung in das lokale radiotherapeutische Vorgehen des limitiert metastasierten Mammakarzinoms zusammen.

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Introduction

Breast cancer is by far the most frequent cancer among women, with an estimated 1.38 million new cancer cases diagnosed in 2008 (23% of all cancers), and it is now the most common cancer both in developed and developing countries. The range of mortality rates is lessened by the more favorable survival of breast cancer in developed regions. As a result, breast cancer ranks as the 5th cause of death from cancer overall (458,000 deaths), but it is still the most frequent cause of cancer death in women in both developing (269,000 deaths, 12.7% of total) and developed regions where the estimated 189,000 deaths is almost equal to the estimated number of deaths from lung cancer (188,000 deaths) [1]. 30–40% of all patients develop distant metastases during the course of their disease [2], and the number of patients with isolated metastases that are eligible for surgical resection is estimated to be relatively small [3].

Hypotheses about Oligometastases

For many years, metastatic breast cancer was generally considered as an incurable disease. However, metastatic breast cancer represents very heterogeneously from a solitary metastatic lesion to diffuse and multiple organ involvement. Retrospective analyses of single institution experiences provide evidence that selected patients with an isolated metastatic lesion or few metastases (so-called oligometastases), who are treated with aggressive combined-modality therapy, may remain disease-free over more than a decade without ever developing additional metastatic deposits [4]. It remains unclear whether this is due to a selection of patients with favorable prognostic factors or whether it can be considered as a treatment result. The term oligometastases, literally interpreted as 'few metastases', was introduced by Hellmann and Weichselbaum in 1995 [5]. Oligometastatic disease has been hypothesized as a clinical state in which the full metastatic potential is not reached and local therapy may offer cure in some patients [5–10]. The authors proposed a clinically significant oligometastatic state to be an intermediated form with limited in number and location metastasis, representing an early course in the chain of metastatic progression amendable by application of a curative therapeutic strategy [5] (table 1).

Is Oligometastatic Disease Curable? Lessons from Other Disease Sites

The hypothesis that local therapy, if added to an effective systemic treatment, may improve survival is supported by findings in another tumor type. In Ewing's sarcoma, the benefits of applying local radiotherapy to metastatic lesions has been convincingly demonstrated; in patients with lung metastases at diagnosis, additional consolidating total lung irradiation was able to increase 5-year survival rates from 20 to 40% [11, 12]. In patients with metastases confined to the bones, the combination of intensive chemotherapy and radiotherapy of metastatic lesions has yielded promising survival figures in phase I/II trials. According to preliminary experience in this disease, the addition of local therapy to standard systemic treatment and intensification of local therapy are of equal if not higher value than intensification of chemotherapy [12–14].

The positive effect of additional local therapy to metastatic lesions has also been evaluated in colorectal cancer. At the time of diagnosis, about 25% of patients present with metastases, and more than one third of patients will develop metastatic disease after curative resection of the primary tumor in the further course of the disease, mainly liver metastases. Patients with a single or few liver or lung metastases should

	Early disease	Locally advanced disease	Oligometastatic disease	Metastatic disease
Disease extend	small primary tumor, no lymph node metastases	large primary tumor, lymph node metastases	solitary or few metastatic lesions	multiple organ involvement
Chance of cure	high (90%)	medium (50%)	zero?	zero
Treatment intent	curative	curative	curative?	palliative
Type of treatment	locoregional + adjuvant systemic	locoregional + adjuvant systemic	systemic + local?	systemic

Table 1. Oligometastatic disease representing a specific condition between locally confined curable disease and incurable metastatic disease

Table 2. Theoretical concept of combining systemic and local therapies in oligometastatic cancer

Diagnostics	The tumor load must be determined as precisely as possible (computed tomography, magnetic resonance imaging, positron emission tomography etc.) to exclude disseminated disease and exactly define the targets of local therapy.
Systemic control and therapy	It is anticipated that the disease can be systemically be controlled. Occurrence of new lesions is unlikely. Control of visible lesions will impact on the further course of disease.
Local therapy	Effective local therapy with minimal side effects is available.
Multimodal treatment concept	Systemic and local therapy can be combined without hindering each other.

undergo curative-intent resection of their metastases, with a resulting chance of long-term cure in the range of 30–40% [15]. In 1986, Hughes et al. [16] published a multi-institutional trial of 607 patients who had received curative resection for liver metastasis from colorectal cancer with 25% of patients disease-free at 5 years, whereas in 1996, Nordlinger et al. [17] reported 1,568 patients who underwent liver resection for metastasis with a 5-year survival rate of 28%. In unresectable disease, palliative chemotherapy aims to prolong survival while preserving or improving quality of life. In the past, the border between a potentially curative and a palliative approach was therefore mainly determined by resectability.

Table 3. Prognostic parameters in patients treated with high-dose chemotherapy for relapsed breast cancer ± local therapy to metastatic sites showing irradiation of metastatic lesions to be the only relevant therapy-related parameter (relapse-free interval, type of adjuvant treatment, pharmacokinetics of high-dose chemotherapy not significant [20])

	Relapse-free survival, %	p[a]
Her-2 status		0.003
Negative	71	
Positive	27	
Initial nodal status		0.01
1–3	74	
> 3	36	
Radiotherapy of metastatic lesions		0.01
Yes	63	
No	18	
Hormone receptor status		0.02
Positive	62	
Negative	33	
Category of primary tumor		0.02
pT1	73	
pT2	52	
pT3	64	
pT4	0	
Number of metastatic lesions		0.03
1	63	
> 1	29	
Site of metastatic lesions		0.11
Local	67	
Distant	59	
Both	27	
Surgery of metastatic lesions		0.73
Yes	56	
No	52	

[a]Univariate analysis.

Table 4. Impact of locoregional treatment on survival in patients with primarily metastatic breast cancer [48]

	Systemic therapy alone	Systemic therapy plus LRT	p
Total, n	261	320	
Type of LRT, n (%)			
Radiotherapy alone	(26.7)	249 (78)	
Surgery + radiotherapy		41 (13)	
Surgery alone		30 (9)	
3-year overall survival, %		43.4	0.0002

LRT = Locoregional therapy.

Recently, a variety of non-surgical local ablative therapies, especially stereotactic radiotherapy or radiofrequency ablation, have been developed, and the question has arisen whether a subset of patients with a limited number of metastases might benefit from the addition of such local treatment. From a theoretical point of view, this concept requires a multimodal diagnostic and therapeutic strategy based on the individual course of disease (table 2).

Molecular Investigations of Oligometastases

Investigations of the molecular biology of oligometastases are very limited. Cillo et al. [18] described that clones with high metastatic potential were more resistant to chemotherapy than cells derived from clones of low metastatic potential. Furthermore, Khodarev et al. [19] used the B16F1 mouse melanoma model and reported that repeated passage through the lungs evolved a more 'aggressive' phenotype defined by increased efficiency in lung colonization and resistance to radiotherapy and chemotherapy of the more highly metastatic clones [7].

Local Therapy in Metastatic Breast Cancer

Treatment concepts in breast cancer have over the past decades been dominated by the hypothesis that breast cancer behaves always like a systemic disease. In the past years, however, it has been clearly demonstrated that improvement of local control impacts on survival in locoregionally confined disease. Results from a variety of retrospective investigations suggest that even in breast cancer the addition of local therapy (especially radiation therapy) to metastatic sites may be associated with better survival [20, 21]. In the analysis by Nieto et al. [20], the addition of radiotherapy to metastatic lesions was the only therapy-related prognostic factor in patients undergoing intensive chemotherapy for relapsed breast cancer (table 3). Moreover, a retrospective investigation has recently shown that addition of locoregional treatment to systemic therapy improved survival in patients with advanced locoregional disease and metastases at diagnosis. This study found that radiotherapy as locoregional treatment was effective in combination with surgery and also if administered exclusively without surgery (table 4). Moreover, patients with oligometastases, who achieve long-term local control after palliative irradiation to metastatic sites, seem to have prolonged survival times [22]. Nevertheless, an additional systemic treatment would possibly be necessary, 73% of patients with oligometastatic breast cancer developed further sites [23]. In summary, these findings have challenged the dogma that metastatic breast cancer is always incurable and have raised the question whether selected patients with limited metastases may be cured [24].

Local Treatment Options in Oligometastatic Breast Cancer

Surgical resection is surely a potentially curative treatment in patients with single metastases of breast cancer [3]. More recently, however, the use of radiotherapy including stereotactic radiotherapy and radiofrequency ablation offers a less invasive approach and could provide a potentially curative treatment of oligometastases [25–31]. Data from recent prospective trials demonstrate that high-precision radiotherapy techniques provide local control rates which are at least comparable to resection [30, 31].

Combining Irradiation and Systemic Therapy

In patients with locally advanced breast cancer, best results are achieved by combining local radiation and systemic therapy [24, 32]. Although some in vitro experiments [32–34] demonstrated a decreased sensitivity to ionizing radiation after incubation of MCF-7 cell lines with tamoxifen, an antagonistic effect of ionizing radiation and treatment with tamoxifen has not been confirmed in animal studies [35, 36]. In contrast, several large randomized clinical studies [37] comparing adjuvant tamoxifen, radiation therapy and placebo, and combined radiation therapy and tamoxifen demonstrated best results [38]. Thus, the experimental endpoints of the in vitro studies may not have been relevant for the in vivo situation, and there is no clinical data for an adverse effect of combined tamoxifen and radiation. Instead, the clinical data argue for a synergistic effect.

Radiotherapy

3D conformal radiotherapy is now widely available and clearly indicated as standard treatment in patients undergoing radiotherapy for oligometastatic disease [5, 39–41]. The benefit of these techniques is substantial in metastatic disease because the target volume includes only the metastatic lesions without any need for adjuvant irradiation of large normal tissue volumes. This leads to a significant reduction in the radiation dose delivered to the surrounding healthy tissue (fig. 1), which tends to be dose-limiting and preclude application of potentially curative doses as well as concomitant radiosensitizing chemotherapy, and allows safe delivery of curative doses even in intense systemic regimens. More recent techniques with increased precision for treatment set-up und delivery are sparing stereotactic radiotherapy techniques and image-guided radiotherapy (IGRT). Stereotactic techniques use an external coordinate system for treatment set-up. This technique has been well established for brain metastases and is now also used for treatment of extracranial lesions (stereotactic body radiotherapy, SBRT). As a result of the precise

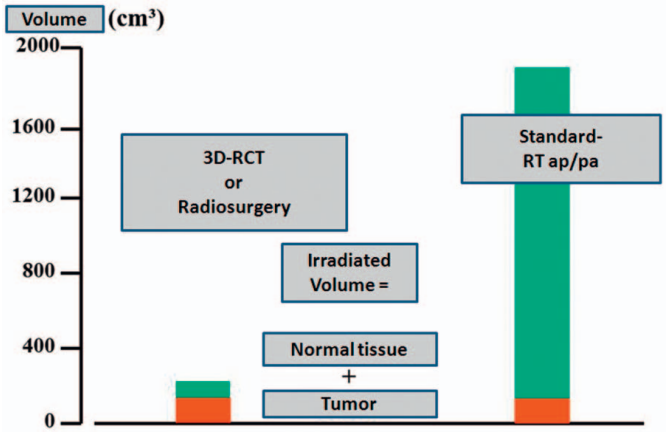

Fig. 1. Impact of 3D conformal radiotherapy (RCT) versus 'older' techniques on normal tissue radiation dose. In patients with 3 target volumes (e.g. 3 metastatic lesions), the gross tumor volume lies in the range of 100–150 cm³. If simple treatment techniques are used (e.g. anterior-posterior opposing portals), a large amount of normal tissue receives the target dose. If conformal treatment techniques are used, the volume of irradiated normal tissue, and hence the risk of acute (and late) side effects, can be dramatically decreased.

treatment set-up, high single doses per fraction (so-called radiosurgery) or hypofractionated regimens can be used. All recent series show promising local tumor control rates in the range of 80–90% [42–44]. The prospective evaluation of SBRT as a therapy approach for liver and lung metastases of different primary cancers including breast cancer was the aim of 3 investigations by Rusthoven et al. [30, 31] and Lee et al. [27]. In a multi-institutional phase I/II trial of SBRT in 47 patients with any primary tumor (4 breast cancer patients) and 1–3 liver metastases, patients received 36–60 Gy in a dose escalating scheme. 63 lesions were treated, mostly smaller than 3 cm in diameter. Rusthoven et al. [30] reported an excellent 2-year rate of local control (92%) and for lesions 3 cm or less an outstanding 2-year rate of local control of 100%. Grade 3 and higher toxicity occurred in only 2% of the patients [30]. In a second multi-institutional phase I/II trial of SBRT, Rusthoven et al. [31] focused on lung metastases of varying primary origin (2 breast cancer patients). In this trial, the authors treated 38 patients with 1–3 lung metastases smaller than 7 cm with 48–60 Gy in a dose-escalating scheme. Local control at 1 and 2 years after SBRT was 100% and 96%, respectively. The poor overall survival (median 19 months) was associated with multiple criteria of unfavorable prognosis; the incidence of grade 3 toxicity was 8%. The phase I study of individualized SBRT of liver metastases by Lee et al. [27] included 68 patients (12 breast cancer patients) with significantly larger liver lesions compared to other trials. The median SBRT dose was 41.8 Gy (range 27.7–60 Gy); the individualized radiation dose was based on the nominal risk of radiation-induced liver disease for 3 estimated risk levels (5, 10, and 15%). The 12-month local control rate was 71%, the

median survival rate 17.6 months. In a prospective pilot study, Milano et al. [45] analyzed curative-intent SBRT in patients with 5 or less oligometastatic lesions. 121 patients (39 breast cancer patients) with ≤ 5 detectable metastases were enrolled and treated with 10 fractions of 5 Gy. The 2-year and 4-year patient local control rates were 67 and 60%, respectively. The 2-year overall survival, progression-free survival, and distant control rates were 50, 26, and 34%, respectively; the respective 4-year rate values were 28, 20, and 25%. A further study conducted by Milano et al. [46] for oligometastatic breast cancer patients with ≤ 5 metastatic lesions treated with curative-intent SBRT led to a 2-year and 4-year local control of 80%, progression-free survival of 38%, and overall survival of 59%. Milano et al. [47] also analyzed the effects of gross tumor volume and primary cancer site. In this analysis, a greater net tumor volume was predictive of significantly worse survival and disease control, whereas breast cancer as the primary lesion was a favorable predictor of survival and disease control.

Conclusions

The role of radiotherapy in metastatic disease has evolved from palliative to potentially curative intent for truly localized oligometastases. For these reasons, enhancing local control of metastatic lesions by means of 3D conformal radiotherapy (with concomitant application of systemic therapy) is a promising strategy for patients with oligometastatic breast cancer. In the last decade, different patterns of highly conformal radiotherapy (SBRT, IGRT, radiosurgery) emerged as potentially curative therapeutic strategies for localized lesions. Introduction of SBRT to multimodal treatment led to excellent response rates and local control rates of up to 2 years. Its effects on progression-free and overall survival are still pending questions especially in comparison with resection or ablative approaches such as radiofrequency ablation. It raises the questions of whether we can truly reach ablation by use of (stereotactic body) radiotherapy, and whether we can cure the subgroup of patients with oligometastases. Breast cancer patients can have a prolonged course of disease, but further studies are needed to assess the impact of different methods of radiotherapy as curative-intent local therapy for patients with truly limited metastatic breast cancer.

Disclosure Statement

The author declares no conflict of interest.

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