Radiotherapy in patients with metastatic breast cancer

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Introduction

Radiotherapy in metastatic breast cancer is aimed at palliation of symptoms and prevention or improvement of functional deficits. The majority of randomised controlled trials focus on the effect of different fractionation regimens and total radiation doses in the treatment of bone and brain metastasis, and spinal cord compression. Breast cancer patients were well represented in these trials and showed usually considerably better outcome than most other investigated cancers, indicating that metastatic breast cancer is a radiosensitive disease. Typically, about 80–90% of patients with metastatic breast experience significant clinical response to local radiotherapy [1,2]. None of these trials had a control arm without radiotherapy. Overall survival was either not investigated or a secondary end-point with the exception of trials on brain metastasis. Randomised trials on the potential impact of local radiotherapy of primary tumours with or without surgery or asymptomatic distant metastasis on survival have not been conducted. Keeping in mind these limitations, the possible impact on survival of local radiotherapy to the primary site and distant metastasis will be briefly reviewed in the following.

Impact on survival of local radiotherapy of the primary tumour site with or without the regional lymph nodes

Radiotherapy to the breast or axillary, infra- and supraclavicular lymph nodes in metastatic breast cancer is often recommended to prevent or relieve symptoms, but is traditionally not considered to have an impact on survival [3,4]. However, several retrospective studies on breast cancer [5–12] and one randomised trial on renal cancer [13] suggest that local treatment of the primary tumour, usually done by surgery, improves overall survival. The data on surgical treatment of the primary site are reviewed in a separate manuscript in this education book [14], whereas in the following the focus is on the available data on radiotherapy of the primary site with/or without surgery.

Le Scodan and colleagues [12] retrospectively reviewed the clinical outcome of 581 patients with metastatic breast cancer of whom 320 received locoregional treatment after diagnosis of distant metastasis. Locoregional therapy consisted of exclusive radiotherapy in 249 patients (78%), surgery of the primary tumour with adjuvant radiotherapy in 41 patients (13%), and surgery alone in 30 patients (9%). At a median follow-up time of 39 months, the three-year overall survival was 43.4% with locoregional treatment of the primary, but only 26.7% without locoregional therapy ($P < 00002$), accounting for a substantial gain in median survival time of 11 months (Fig. 1). The survival benefit in favour of locoregional treatment was particularly marked in women with visceral metastases, whereas no survival advantage was observed in patients with bone metastases. Treatment of the primary site was an independent prognostic factor in multivariate analysis (hazard ratio: 0.70; 95% CI, 0.58 to 0.85; $P < 0.0002$, Table 1). Radiotherapy included the breast or chest wall and the infra- and supraclavicular lymph nodes in most patients. The mean radiation dose was 48.7 Gy administered in most patients within 4–5 weeks. The majority of patients, who did not undergo surgery breast surgery (n = 249), received a booster dose of an average of 23 Gy of radiotherapy to the primary site, using different techniques.

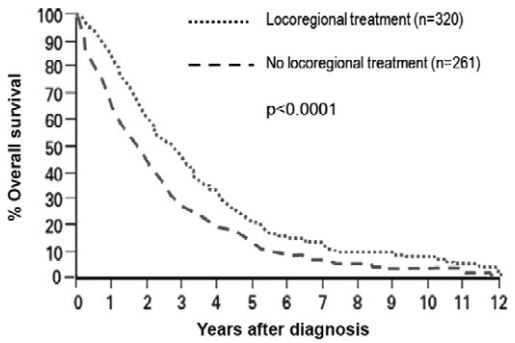

Fig. 1. Influence on overall survival of locoregional treatment to the primary tumour with or without regional lymph nodes in metastatic breast cancer. (After Le Scodan et al. [12].)

Table 1
Multivariate analysis of prognostic factors in survival of metastatic breast cancer (Cox model, n = 564)[a]

Parameter	Hazard ratio	95% CL	p
Multiple metastases vs. solitary metastase	1.60	1.30–2.00	<0.001
Hormonal treatment +/– CHX vs. CHX	0.53	0.40–0.70	<0.001
Age: 24–54 y vs. 55–94 y	1.27	1.10–1.60	0.003
Visceral metastasis: yes vs. no	1.27	1.00–1.60	0.03
cN1–3 vs. cN0	1.50	1.20–1.85	0.003
Locoregional treatment: yes vs. no	0.70	0.58–0.85	0.002

[a]After Le Scodan et al. [12].
CL, confidence limits.

Interestingly, the median survival times and three-year overall survival rates were 26 months and 46% (95% CI, 29.6–63.6%) for the 30 patients treated with surgery alone, 31 months and 41.5% (95% CI, 35.5–47.9%) for the 249 patients treated exclusively with locoregional radiotherapy, and 39 months and 52.6% (95% CI, 37.6–67.2%) for the 39 patients treated with surgery followed by radiotherapy respectively ($P = 0.07$). Although this was a retrospective analysis and only a few patients were treated with surgery alone, these observations are compatible with the hypothesis that improved locoregional tumour control achieved by combined treatment may result, analogous to non-metastatic breast cancer, in a survival benefit. However, in the absence of randomised trials, one cannot exclude, neither for surgery nor for radiotherapy, a prescription bias in that physicians may have recommended local therapy more frequently to patients with a low metastatic tumour burden, younger age, and better performance status. Multivariate analysis is be able to partly compensate for these biases, but cannot be regarded as a substitute for randomised trials. At this time, the patient population that benefits most from locoregional therapy in the metastatic setting remains undefined. Initial considerations that patients with a relatively good prognosis, e.g., with bone metastases only, will have the largest advantage from local treatment have been challenged by the observation of Le Scodan and colleagues [12], which indicates the opposite.

Different mechanisms have been discussed, how locoregional treatment of the primary site can prolong overall survival. Uncontrolled local disease may induce oedema, infection, and thromboses with sometimes life-threatening consequences and the persistent primary tumour could be a source of continuous seeding of new distant disease. Recent experimental data indicate that radiation-induced tumour cell necrosis can result in an improved dendritic cell-mediated antitumoral immune response [15]. Based on the available data, no general recommendations can be given for the locoregional treatment outside of clinical trials.

Impact on survival of radiotherapy for brain metastasis

The development of brain metastases is typically a late event in the progression of metastatic breast cancer. Brain metastases as the sole site of distant disease is still quite uncommon, but has been observed more frequently after the introduction of trastuzumab as adjuvant treatment for Her2neu-positive disease [16], presumably as a consequence of the lack of efficiency of trastuzumab for microscopic disease behind the blood–brain barrier. In a multi-institutional database of 4259 patients with newly diagnosed brain metastases of different cancers [1], the median survival of breast cancer patients was 11.9 months (n = 642), which is considerably longer than the average of to 7.2 months for all patients in the database. For patients with multiple brain metastases (>3 lesions) whole brain radiotherapy remains the standard of care. Different fractionation schedules and total radiation doses have been tested in a number of randomised trials showing little differences in terms of neurological symptom improvement and overall survival among 2×8 Gy, 5×4 Gy, 10×3 Gy, and 20×2 Gy. In a meta-analysis of all published fractionation trials, 10×3 Gy to 30 Gy was shown to be the preferable schedule in terms of toxicity and survival [17]. Since none of these studies had a best supportive care arm, one cannot formally prove that whole-brain radiotherapy improves overall survival. However, median survival in the few documented cases with symptomatic brain metastases receiving exclusively best supportive care was below two months [18,19]. Also, a prescription bias toward selecting the worst cases for best supportive care can

be assumed, the observed large difference in survival in favour of whole-brain radiotherapy gives indirect evidence that radiotherapy prolongs survival for several months. In breast cancer patients with solitary brain metastasis, median survival ranges between 13.8 to 23.7 months after local treatment with surgery or radiosurgery with or without whole brain radiotherapy [1] with approximately 15% of patients being alive at five years after therapy. Recent data indicate that in breast cancer patients with good performance status and Her2/neu +++ disease median survival ranges from 19.5 months [20] to 25.5 months [21], if treated with whole-brain radiotherapy or radiosurgery ($\leqslant$3 lesions) and trastuzumab. Taken together, these observations give evidence for a profound survival benefit from local treatment of brain metastases by radiotherapy.

Impact on survival of radiotherapy to bone metastasis

Bone metastasis is one of the most frequent sites of distant disease in breast cancer. Radiotherapy results in significant pain relief in the irradiated region in approximately 80% and complete pain relief in about 30% of patients, and induces re-calcification within 3–6 months in the majority of cases. Randomised trials have compared different fractionation schedules and total doses ranging from 1×4 Gy to 15×2.7 Gy, the most frequently tested schedules being 1×8 Gy and 10×3 Gy [22]. In none of these studies were significant differences in terms of pain control observed between the testes radiation schedules, and only one study showed a lower frequency of pathological fractures at a higher total dose. Most studies included a significant proportion of breast cancer patients in addition to other cancers, particularly lung cancer, but only a few studies presented the results by tumour type. The median survival of breast cancer patients with bone metastases ranged from 11 months [23] to 16 months [24]. In none of these studies were significant differences in survival reported. Although survival was not the primary end-point in any of these studies and survival of breast cancer patients was not separately reported for different treatment arms, there is little doubt that this observation is also true for breast cancer patients. Since a control arm with no radiotherapy was not used for comparison in any of these studies, one can neither prove nor disprove that radiotherapy of bone metastases results in a survival advantage for breast cancer patients. Prevention of pathological fractures that could cause lethal complications, represents a conceivable mechanism for how local treatment of bone metastases prolongs survival. However, this concept is not substantiated by available data. The current knowledge suggests that treatment of bone metastases by radiotherapy does not prolong survival.

Impact on survival of radiotherapy metastatic spinal cord compression

Decompressive surgical resection followed by radiotherapy and exclusive radiotherapy are effective options for retaining or regaining walking ability. In the case of motor deficits immediate treatment is of paramount importance for the functional outcome. Functional outcome in breast cancer patients is excellent, if treated before severe functional loss has occurred. In a matched pair analysis Rades and colleagues [2] compared radiotherapy alone with surgical decompression followed by radiotherapy. They reported local tumour control at 12 months of 89% and 12-month survival of 78% with radiotherapy, regardless of the use of decompressive surgery. One-year overall survival for breast cancer patients was 78%. The results in breast cancer after radiotherapy alone for metastatic spinal cord compression in patients with oligometasatses ($\leqslant$3 bone metastases, no visceral metastases) were even better resulting in 98% local tumour control and 89% survival at 12 months. The same group [25] had reported a 3-year overall survival of 51% in a group of 149 breast cancer patients with oligometastases receiving radiotherapy for spinal cord compression. Valid data on the long-term effects of corticosteroids alone or systemic treatment of breast cancer are not available for this clinical situation. Whether the quite satisfying local efficiency of radiotherapy significantly improves overall survival, cannot be proven in the absence of randomised data. However, one does not need a randomised trial to predict that without local treatment most patients would become bed-ridden within a short time. Being confined to the bed enhances the risk of complications like thromboembolic events and pneumonia. From these considerations one can indirectly conclude that local treatment of spinal cord compression may have the potential to prolong survival.

Impact on survival of radiotherapy of other metastatic sites

Friedel and colleagues [26] were able to demonstrate in a large cohort of breast cancer patients (n = 374) that 10–15 years' long-term survival can be

achieved by complete surgical resection of isolated lung metastases. Since stereotactic radiotherapy of lung metastases has been recently shown to be safe and effective [27,28], stereotactic radiotherapy of lung metastases is an option for selected breast cancer patients with isolated lung metastases that may have the potential to prolong survival. Similar, but less convincing, observations have been published regarding the resection of liver metastases in breast cancer patients [29]. Stereotactic radiotherapy of liver metastases has been established with promising preliminary results [30,31], indicating that stereotactic radiotherapy of liver metastases in breast cancer might also be an option in the near future. This procedure may also have the potential to improve survival in selected patients.

Summary and conclusions

The available clinical data on patients with metastatic breast cancer is compatible with the hypothesis that a local treatment of the primary tumour with or without regional treatment prolongs survival. Prevention of life-threatening local complications and prevention of continuous seeding of new distant disease originating from the primary tumour have been proposed as possible mechanisms that apply for local radiotherapy and surgery. Recently published experimental data indicate that radiation-induced necrosis of the primary tumour may result in an antitumoral immune response. However, no data from randomised trials are available and the substantial survival benefits observed in retrospective comparisons may have been influenced by a number of biases. For the time being, the decision whether or not to integrate locoregional treatment of the primary tumour into the therapeutic concept needs to be done on an individual basis.

In principle, the identical mechanisms described above also apply for local treatment of distant metastases in metastatic breast cancer. Clinical experience in the local treatment of acutely life-threatening distant disease, for example, in symptomatic brain metastasis, undoubtedly suggests a prolongation of survival, particularly in the case of response to treatment. Aside from this situation, clinical trials and retrospective comparisons of local treatments of distant metastases in metastatic breast cancer typically compared different radiation schedules with or without additional surgery in symptomatic patients, without utilising a control group. As a result, a general survival benefit from the local treatment of distant metastasis has not been scientifically proven and should be the subject of further investigations.

Conflict of interest statement

The author has no potential conflict of interest to disclose.

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