Chapter 7

Radiotherapy for oligometastases

(Original in Dutch: Radiotherapie bij oligometastasen)

Gwendolyn H.M.J. Griffioen, MD, Max Dahele, MBChB, PhD, Cornelis, J.A. Haasbeek, MD PhD, Ben J. Slotman, MD, PhD

Department of Radiation Oncology, VU University Medical Center, Amsterdam, the Netherlands

Summary

The radical treatment of limited volume ‘oligometastasized cancer’ with high doses of radiotherapy, can achieve a high probability of local control. Non-randomized studies suggest that in some patients this treatment strategy is associated with promising survival. In the absence of randomized studies, we present a pragmatic approach for this patient group. This is based on multidisciplinary evaluation and discussion with the patient of the limited evidence and alternative options, possible benefits, uncertainty about the effect on prognosis, and toxicity of the treatment.
Introduction and definition of oligometastases

The treatment of patients with oligometastases is an emerging, rapidly evolving and controversial topic in daily oncological practice. The term ‘oligometastases’ was first used to describe a possible separate stage of cancer by Hellman and Weischelbaum in 1995. It refers to a stage between localized cancer and extensively metastasized disease, in which both the number of metastases as well as the number of organs in which these metastases are located, are limited. The importance of an oligo-metastatic situation is that effective local treatment of these metastases could result in a better prognosis. In some of these patients cure, or at least long-term survival, may be possible. As a result, radical treatment of oligometastases, instead of, for example, only symptomatic treatment with chemotherapy or conventional radiotherapy, is becoming increasingly popular. For some tumor sites, this new approach has already been included in national protocols. Examples include the resection of liver metastases in colorectal carcinoma and radiosurgery for brain metastases.

The term ‘oligometastases’ is, however, not clearly defined for most tumors. In most cases, it is defined as a maximum of 5 metastases, regardless of the type of primary tumor. A problem with this simple approach, only based on the number of metastases, is that many patients are found to progress in other locations and therefore not to have benefited from aggressive treatment. Sub-optimal diagnostic criteria, including unknown molecular characteristics, and over-optimistic physicians, are possible reasons why relatively few patients are currently properly identified as truly ‘oligo-metastatic’.

With the introduction of stereotactic body radiotherapy in 2003 in the VU University Medical Center, a start was also made with treating patients with oligometastases in various locations. This now includes for example, metastases to the lung, liver, lymph nodes, and vertebrae, and patients are being referred from a number of Dutch hospitals. Despite the fact that the total number of patients treated is relatively small in comparison to other standard indications for radiotherapy, it continues to increase. In this brief review, we will provide a literature background regarding radical radiotherapy for oligometastases, discuss on a number of new developments.
in this field and conclude with some practical suggestions. As the treatment of oligometastases is a broad topic, it was necessary to limit ourselves to a selection of the literature.

**Initial experiences**

Surgery has a long history in the radical treatment of metastases, with the literature on the removal of metastases dating back more than 100 years. One of the first attempts to surgically remove a lung metastasis, is attributed to Sedillot in 1855, who, during the resection of a tumor in the chest wall, also removed a lung metastasis. In the final 2 decades of the last century, major surgical registration studies were published, showing a link between a prolonged survival and the surgical resection of lung (> 5000 patients with several different primary tumors) and liver metastases (> 800 patients with colorectal tumors).²³ About a third of the patients in these non-randomized studies, were still alive after 5 years. From the registration study for lung metastases, some favorable prognostic factors emerged, including a complete resection, diagnosis of germ cell tumors, a disease-free period of ≥36 months after initial diagnosis and having a solitary metastasis.²³ The series on resected liver metastases showed the following prognostic factors for improved survival: disease-free interval >12 months, 1-2 metastases, smaller volume of metastases, lower stage of the primary tumor, a wide resection margin, and the absence of pathological lymph nodes and synchronous extra-hepatic metastases.⁶

These and other studies support the now prevailing hypothesis that there is a group of patients who, despite the presence of metastases, can still achieve prolonged survival with local treatment. The favorable results have also made it more difficult to conduct randomized studies, in part because some now regard this as unethical for certain patient groups.

**Radiotherapy for oligometastases**

Alternatives to surgery have been used for the radical local treatment of metastases, including radiotherapy. An early example concerns the treatment of brain metastases with stereotactic radiosurgery, in which a single fraction of high-dose radiation is administered with high precision.⁷ However, extracranial metastases were soon also being treated with stereotactic radiotherapy (‘stereotactic body radiotherapy’ [SBRT] or ‘stereotactic radio ablative therapy’
Radiotherapy for oligometastases

[SABR]), in which a high-dose of radiation is given in a small number of fractions (for example, up to 5-8) (Figure 1). The fact that these approaches are effective for intra- and extracranial metastases, was reported in the 1990's, for example in two publications from the Karolinska Hospital. These studies showed a local control of 80% for extracranial metastases and >90% for intracranial metastases. Many other, especially retrospective or prospective phase I / II studies, have followed for metastases in various organs. A selection of these studies are shown in Table 1. More conventional fractionated radiotherapy with a high total dose, but given in multiple fractions (for example, 15-20 or more) and with high precision, can in some cases be a good alternative, for example, because of the proximity of critical structures or depending on the available radiotherapy techniques.

Figure 1. Stereotactic radiotherapy for a solitary FDG PET positive para-aortic lymph node metastasis after previous nephrectomy on the right hand side (1A). In this case, 8 fractions of 7.5 Gray were prescribed, covering the majority of the target area with further dose escalation within the lymph node. The individual lines represent specific (iso)doses (outer lines lower than the inner lines). By using intensity modulated radiotherapy the dose conforms around the remaining left kidney and ureter in order to relatively spare these critical organs. Radiotherapy was image-guided to increase the precision. Figure 1B shows a "cone-beam" CT (CBCT) image made with the treatment device at the time of treatment. The CBCT is used to position the patient. Different structures, such as the target area (lymph node), kidney and ureter (within the black line) are visible on the CBCT. FDG-PET-CT scan 15 months after irradiation showed no FDG activity at the location of the lesion, or elsewhere in the body.

The data summarized in Table 1 shows that good results can be achieved using radical radiotherapy for oligometastases in some patients. In these selected studies, the local control of the irradiated lesion is typically good and the toxicity of the treatment is limited. A recent review article suggests that around 20% of the treated patients are disease-free with a follow-up of 17 to 48 months. This supports the idea that radical radiotherapy may have a beneficial effect for some of the patients. However, in all the above-mentioned studies, the majority of the patients were treated for only 1 or 2 metastases and data on the
quality of life after this treatment are limited. In addition, randomized studies or other studies with good control groups are lacking. This makes it difficult to determine whether the treatment, in addition to a good local control, actually improves survival.

**Prognostic factors**
Since only some of the treated patients seem to have long-term benefits from the radical treatment of oligometastases, selection probably plays an important role in a good outcome. The following prognostic factors may be of importance in the selection of appropriate patients.

*Primary tumor, and localization of metastases*
A number of publications show that some primary tumors are associated with a better survival. One study reported that patients with oligometastases from breast cancer had a better prognosis than those with oligometastases from lung or colon carcinoma. This also seems to apply for metastases within a same organ. Patients with liver metastases from colorectal or breast cancer, for example, showed a better survival than patients with liver metastases from lung and ovarian carcinoma. Furthermore, tumors with certain mutations may have a different prognosis in the metastatic setting, than patients with the same type of cancer without this mutation. For example, patients with lung cancer and an EGFR mutation, or patients with breast cancer and a positive HER2 receptor.

*Disease-free interval, size and number of metastases*
As previously seen in surgical studies, irradiated patients with a longer disease-free interval between the diagnosis of the primary tumor and its metastases seem to have a more favorable survival. Furthermore, a smaller volume and a smaller number of metastases also seem to be associated with a better survival.

*Radiation dose*
Finally, patients who are given a higher dose of radiation seem to have a better local control and therefore perhaps a higher chance of an improved prognosis.

The optimal dose for different locations is not yet completely clear, and as can be seen in Table 1, several radiation schedules are used. An important
reason for this is the difference in tolerance for radiotherapy of the surrounding healthy tissues, which are dependent on the location of the metastasis.  

Figure 2. Stereotactic radiotherapy for a solitary choline PET positive spinal metastasis of prostate cancer. In this case a treatment scheme of 3 fractions of 10 Gray (Gy) was chosen, instead of, for example, one fraction of 20 Gy, to reduce the estimated biological equivalent dose in the normal tissues while giving the same biologically equivalent dose to the tumor. The contours in the axial image (2A) show the esophagus / stomach and the left kidney. The shaded area represents a total dose of at least 24 Gy in 3 fractions. This dose is located outside the spinal canal (2A + B), which is relatively spared. Follow-up was based on the prostate specific antigen (PSA) and, unfortunately, within one year of treatment an increase in the PSA was seen. On a new choline PET-CT, multiple metastases were found outside the (locally controlled) irradiated area.

Developments

Combination with systemic therapy

The optimal timing and combination of local and systemic therapy has not been studied well. Studies in patients with metastatic disease who are treated with systemic therapy alone, show that a portion of these patients may sustain long-term survival. This raises the question whether the long-term survival is achieved by the local treatment, the systemic treatment or by a combination of both. In daily practice, in order to prevent an increase in toxicity, chemotherapy is stopped during stereotactic radiotherapy. In some patients, systemic therapy may be stopped indefinitely if all lesions receive definitive local treatment. Another possibility is that local therapy can be used to delay systemic therapy if it has not yet been started. Hormonal treatment is not always stopped during radiotherapy. The experience with so-called “targeted therapy” is an evolving situation, and the side effects when combining these with stereotactic radiotherapy is not yet known. In our center, targeted agents are generally not administered concurrently during ablative radiotherapy, and are they stopped for a short period before and after irradiation.
Variants of oligometastatic disease

Instead of only distinguishing patients on the basis of the number of metastases, prognostic sub-groups with oligometastases are being identified.\(^\text{21,35}\)

1. Patients who present with a limited number of metastases and in whom the primary tumor is not yet treated (synchronous oligometastases).\(^\text{20,36,37}\)

2. Patients in whom the primary tumor has been treated and who are subsequently diagnosed with oligometastases (metachronous oligometastases or oligorecurrence). This group can be further divided into patients in whom the primary tumor is under control and patients in whom the primary tumor shows progression.\(^\text{35}\)

3. Patients with previous (oligo)metastases, which received treatment, in whom new oligometastases are diagnosed during follow-up (oligo-progression).\(^\text{34}\) Recent studies suggest that approximately 80% of patients treated for oligometastatic disease show progression (elsewhere) and that in some of these patients, the progression is limited in number and in terms of location of the metastases.\(^\text{18,19,21}\) In this scenario, repeated radical treatment has been associated with good results in selected patients.\(^\text{19}\) By repeatedly treating oligometastases, cancer may be converted into a chronic disease in some patients. This has consequences for follow-up strategies including periodic imaging.

4. There are also a group of patients with multiple metastases, in whom, after a response to systemic therapy, only a few metastases remain visible (oligo-persistent disease). Stereotactic radiotherapy has been proposed as a strategy to improve treatment results in this group as well.\(^\text{38}\)

Current clinical trials

Because most data comes from relatively small, non-randomized studies, caution is required regarding the conclusions. If randomized trials are not feasible in certain patient groups, there may be a role for registration studies and pooled data analyses to strengthen the evidence for this treatment.\(^\text{39}\) In addition, besides the effects on survival, the effects of treatment on quality of life, and cost advantage or disadvantages are often not, or not entirely, known.

A search on “www.clinicaltrials.gov” using the search terms ‘oligometastases or oligometastasis or oligometastatic’ did not show any ongoing phase III trials. There are 13 phase II trials, of which one is accruing patients in the
Netherlands. This is the ‘Stereotactic Ablative Radiotherapy for the Treatment of Comprehensive Oligometastatic disease’ (SABR-COMET) trial (NCT01446744). In this study, which was initiated by the VU University Medical Center and the London Ontario Cancer Center in Canada, patients with 1-5 oligometastases are randomized between standard palliative treatment (e.g., chemotherapy and/or low-dose radiotherapy), and stereotactic radiotherapy to all metastases.\textsuperscript{40}

Two recent randomized trials for patients with oligometastases from non-small cell lung cancer (NCT00776100, NCT00887315) have closed because too few patients could be accrued. Based on trials being unsuccessful because of a disappointing inclusion rate, some investigators have concluded that such studies are doomed to fail in the future as well.\textsuperscript{41} Many physicians (primary care providers, radiotherapists, multidisciplinary teams), but also patients, seem to have trouble with the randomization. A second factor making randomization in this group of patients difficult, is the increasing availability of radical treatment of metastases outside study protocols. In practice, patients do not necessarily need to participate in a study to get the treatment.

\textbf{Suggestions for daily practice}

When treating patients with oligometastases with radiotherapy outside a study protocol, we offer the following practical approach:

(1) Adequate staging, including FDG-PET-CT of the whole body for PET-positive primary tumors, MRI brain (consider for metastases of tumors which frequently metastasize to the brain (such as lung cancer), and, whenever possible, pathological confirmation (including appropriate molecular research).

(2) Discussion of the case in a tumor-specific multidisciplinary team (MDT), in which all treatment options are discussed and a decision is made on what the best treatment option is thought to be for this individual patient; e.g. radiation therapy, systemic therapy, surgery, radio-frequency ablation (RFA), or watchful waiting. Factors such as previous treatments, patient performance score, morbidity, tumor location and size, and the specific risks and side effects of the intervention should be included in this decision.\textsuperscript{42} Depending on the institutional experience and, where necessary, consider a second opinion or referral to another institution.

(3) If possible, consider forming an ‘oligometastases’ team within the radiation oncology department. Individual patients can be further discussed in this group
with respect to the feasibility of treatment and local/departmental guidelines. The decision on stereotactic or more conventional radiotherapy, for example, depends upon the location of the metastases, the surrounding structures, and any previous irradiation in the same area.

(4) Discussion with the patient about the purpose of the irradiation, the uncertainty about the benefits and the limited evidence.

(5) Follow-up in close coordination with all practitioners. Because imaging after high-dose radiotherapy sometimes is less easy to interpret, consultation with the treating radiation oncologist or within an MDT may be useful. 43,44

(6) Regular review of the published literature and frequent assessment of own results.37

Conclusion

The radical treatment of limited volume ‘oligometastatic’ cancer with high-dose radiotherapy can provide a high probability of local control. Non-randomized studies suggest that this treatment may lead to a prolonged survival in a subset of patients. However, the true effect of local treatment on survival of the patient is not yet clear, and there is a need for additional data from randomized trials, registration studies and pooled data analyzes. At this moment, the treatment approach should be based on a multidisciplinary assessment, and full discussion with the patient about the limited evidence, the side effects and risks, which can be expected from the treatment, as well as the expectations and uncertainties regarding the possible gains in life expectancy and quality of life.
Table 1. Selected articles on radiotherapy for oligometastases, focusing on stereotactic radiotherapy

<p>| Article / anatomic location | Design | Population | Histology | Intervention | Interval from diagnosis of primary tumor | Total dose / fractionation | Overall survival | Local control | Toxicity | Remarks |
|----------------------------|--------|------------|-----------|--------------|------------------------------------------|----------------------------|------------------|---------------|----------|---------|---------|
| Andrews et al. 2004 ¹ Brain | Phase III, RTOG 9508 | 333 pts / 536 metastases 56% of pts had a solitary metastasis In about 3/4 of pts the primary tumor was stable / 'absent' About 2/3 of pts had extracranial metastases | Variable | WBRT vs. WBRT+ SRS | WBRT = 37.5 Gy / 15 fractions SRS = 15, 18 or 24 Gy / 1 fraction | Median OS WBRT vs. WBRT+SRS Overall = 5.7 vs. 6.5 m (p=0.14); one metastasis = 4.9 vs. 6.5 m (p=0.04); solely brain metastases = 8.6 vs. 10.2 m (p=0.52) | 1-year = 82% vs. 71% (p=0.01) | Acute and late toxicity comparable in both groups | Patients in SRS group with a single metastasis, RPA class 1 of whom the largest metastases were &gt;2cm, had a better survival according to univariable analysis. RPA 1 and histology (squamous cell/non-small cell) were significant factors at MVA. 2-year OS was approximately 15% in WBRT+SRS group (vs. approx. 10% with WBRT) |
| Lee et al. 2009 Liver | Prospective phase I, dose-escalation study | 68 pts / median 1 metastasis (1-8) 53% of pts had disease outside the liver | Variable | SBRT | Median 41.4 Gy (27.7-60) / 6 fractions | Median OS = 17.6 m, 2-year OS approx. 40% Median FU = 10.8 m | 1 year = 71% | No radiation induced liver disease (RILD). Grade 2 rib fractures = 2 pts. Late grade 4 toxicity = 2 pt (x1 duodenal hemorrhage; x1 small bowel obstruction by herniation). Late grade 5 = 1 pt (small bowel obstruction by tumor ingrowth) | Patients were inoperable and non-eligible for 'standard' therapy. Patients with a small tumor volume (&lt;75.2 ml) and higher treatment dose had a significant better local control on univariable analysis. No chemotherapy for 2 weeks before until 4 weeks after SBRT |</p>
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<th>Article / anatomic location</th>
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<tr>
<td>Rusthoven et al. 2009 Liver</td>
<td>Prospective phase I-II, dose escalation</td>
<td>47 pts / 63 metastases 45% pts with disease outside liver 72% pts received systemic therapy after SBRT</td>
<td>Variable</td>
<td>SBRT</td>
<td>Median 22.7 m (0-236) of pts 60 Gy / 3 fractions</td>
<td>Median OS = 20.5 m 2-year OS = 30% Median FU = 16 m</td>
<td>1 year = 95% 2 year = 92% (94% of lesions were irradiated with 60 Gy; 100% vs. 77% with max diameter ≤3 vs. &gt;3 cm)</td>
<td>No grade 4-5 toxicity. Late grade 3 = 1 pt with skin lesion treated with surgical intervention and hyperbaric oxygen therapy on trial basis</td>
<td>Median OS in 'unfavourable' histology (lung, ovarian, non-colorectal gastrointestinal tumors) was significant worse vs. 'favourable' histology (including breast, colorectal, kidney, sarcoma) = 12 vs. 32 m (p&lt;0.001) No chemotherapy for 14 days before and after SBRT</td>
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<td>Siva et al. 2010 Lungs</td>
<td>Systematic review</td>
<td>SBRT = 334 pts / 564 metastases (13 studies) SRS = 148 pts / 175 metastases (6 studies)</td>
<td>Variable</td>
<td>SBRT / SRS</td>
<td>Un-known SBRT = 'weighted' 2-years OS 53.7% SRS = 50.3% Median FU SBRT = 8.2-44 m and SRS = 9-22 m</td>
<td>SBRT = 'weighted' grade ≥3, 2.6%. 1 pt with grade 3 esophageal necrosis SRS = no grade 4-5 toxicity. Furthermore, mainly radiation pneumonitis</td>
<td>Multiple dose and fractionation schemes = no clear consensus on optimal treatment. Effect of volume on local control unsure.</td>
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<td>Casamassima et al. 2012 Adrenal</td>
<td>Retrospective</td>
<td>48 pts / 58 metastases (10 pts = bilateral)</td>
<td>Variable</td>
<td>SBRT / SRS (n=40 pts) / SRS (n=8 pts)</td>
<td>Median 37.2 m (0-132) SBRT = mean 12.1 Gy / fraction, with total of 34.9 Gy SRS = mean 23.5 Gy / 1 fraction</td>
<td>1 year OS = 39.7% 2 years = 14.5% Median FU = 16.2 m</td>
<td>1 year = 90% 2 years = 90%</td>
<td>No grade ≥3 1 pt with grade 2 adrenal insufficiency</td>
<td>No significant prognostic factors, possibly secondary to limited number of incidents</td>
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<td>Bignardi et al. 2011</td>
<td>Institutional analysis</td>
<td>19 pts / 11 pts solitary metastasis, 8 pts with 'oligometastases' in multiple locations</td>
<td>Variable SBRT</td>
<td>Unknown</td>
<td>36-45 Gy / 6 fractions</td>
<td>1 year = 93.3%</td>
<td>1 year = 93.3%</td>
<td>2 years = 77.8%</td>
<td>No grade 4-5 toxicity. 1 pt with grade 3 bowel complaints, possibly due to abdominal adhesions (had previous abdominal surgery)</td>
<td>1/2 of pts with tumor diameter &gt; 3 cm No chemotherapy for at least 3 weeks before SBRT and ceased until progressive disease</td>
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<td>Abdominal lymph nodes</td>
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<td>Median FU = 12 m</td>
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<td>2 years = 77.8%</td>
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<td>Gerstzen et al. 2007</td>
<td>Prospective institutional analysis</td>
<td>393 pts / 500 metastases</td>
<td>Variable SRS</td>
<td>Unknown</td>
<td>Mean dose 20 Gy (12.5-25 Gy) / 1 fraction</td>
<td>Median FU = 21 m</td>
<td>'Long-term imaging' local control 88%</td>
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<td>No neurological toxicity</td>
<td>Median tumor volume 29 cm3. The metastasis was previously irradiated in 344 pts</td>
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<td>Spinal</td>
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<td>Wang et al. 2012</td>
<td>Prospective phase I-II</td>
<td>149 pts /166 metastases (not all lesions had extension in the vertebra)</td>
<td>Variable SBRT</td>
<td>Unknown</td>
<td>Total dose 27-30 Gy / typically in 3 fractions</td>
<td>Median OS = 23 m</td>
<td>1 year local control on MRI = 80.5%</td>
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<td>No toxicity of spinal cord. No grade 4-5 toxicity. Grade 3 including nausea, vomiting, diarrhea, fatigue, (all n=1) and chest pain (non cardiac, n=3)</td>
<td>Median tumor volume 38.2 cm3. Approx. 2/3 of pts received prior treatment at this location (radiotherapy / surgery) Significant decrease of pain and opioids. No chemotherapy for at least 30 days before SBRT (hormonal therapy / bisphosphonates allowed)</td>
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<td>Spinal / para-spinal</td>
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<td>2 years OS = 46.4%</td>
<td>2 years = 72.4%</td>
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<td>Article / anatomic location</td>
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<td>Guckenberger, et al. 17 Spinal / para-spinal</td>
<td>Retrospective institutional analysis KPS ≥70 6 pts received post-operative radiotherapy</td>
<td>14 pts = 12 spinal + 2 para-spinal / 16 lesions</td>
<td>Variable</td>
<td>IG-IMRT</td>
<td>0–3.2 years for pts with spinal metastases</td>
<td>Median dose / fractions = 58 Gy / 20 fractions</td>
<td>1 year OS = 85% 2 years OS = 63% Median FU = 17 m</td>
<td>2 years = 88%</td>
<td>No late grade &gt; 2 toxicity</td>
<td>Higher dose administered by fractionates irradiation seems effective</td>
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<td>Salama, et al. 2012 18 Multiple locations</td>
<td>Prospective, dose escalation ECOG ≤2 1–5 extracranial metastases no previous irradiation</td>
<td>61 pts / 113 metastases</td>
<td>Variable</td>
<td>SBRT</td>
<td>Median 11.6 m (0–302) 24–48 Gy / 3 fractions</td>
<td>1 year OS = 81.5% 2 years OS = 56.7% Median FU = 20.9 m</td>
<td>1 year = 67.2% 2 years = 52.7%</td>
<td>No grade 4-5 toxicity</td>
<td>Mean of 2 lesions / pts (55% 1 lesion) 27% of pts had no new metastases during FU No chemotherapy ‘during’ SBRT (hormonal therapy allowed)</td>
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<tr>
<td>Milano et al., 2012 (^\dagger)</td>
<td>Prospective KPS ≥70</td>
<td>121 pts / 293 metastases (7 brain metastases; 286 extracranial)</td>
<td>Variable</td>
<td>SBRT</td>
<td>Un-known</td>
<td>50 Gy / 10 fractions</td>
<td>Breast vs non-breast OS 2 years = 74% vs 39% 4 years = 54% vs 16% 6 years = 47% vs 9% Median FU breast group 4.5 years; non-breast: 1.7 years</td>
<td>Breast vs non-breast 2 years = 87% vs. 74% 4 years = 87% vs. 68% 6 years = 87% vs 65%</td>
<td>No grade 4-5 toxicity. 1 pt with grade 3 non-maligne pleural and cardial effusion</td>
<td>Analysis breast vs. non-breast. In non-breast group tumor volume was prognostic for local control In de breast group all bone lesions remained stable during FU 38% breast and 62% non-breast pts alive &gt;4 years SBRT for local progression/ new lesions Progressive disease during the systemic therapy given prior to SBRT is a negative prognostic factor</td>
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ECOG=Eastern cooperative oncology group, FU = follow-up, IG-IMRT: image-guided intensity modulated radiotherapy, KPS=Karnofsky performance score, m = months, MRI = magnetic resonance imaging, OS = overall survival, pts = patients, SBRT = extracranial stereotactic radiotherapy, SRS = stereotactic radiosurgery (single fraction), WBRT = whole brain radiotherapy
References


