Evaluation of efficacy and safety of robotic stereotactic body radiosurgery and hypofractionated stereotactic radiotherapy for vertebral metastases

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Introduction

Malignant neoplasms were confirmed in 10 million people worldwide in the year 2000. According to the World Health Organization’s (WHO) estimation, in 2015 the number of newly diagnosed malignancies will rise to 15 million [1, 2]. Prevalence of metastatic spread at the time of diagnosis is varied, depending on histopathological type of primary tumour and quality of medical care. Vertebral metastases identified in 30–50% of patients with systemic cancer are detected at higher rates in patients with primary tumours in the breast, lung, prostate and kidney [1, 3, 4]. Moreover, spinal metastases are the most common vertebral neoplasms, diagnosed 20 times more frequently than primary tumours in this localization [1, 5]. Diagnosed in all age groups, most often at age 40 to 70 years, spinal metastatic lesions are described mainly in males [1, 6]. The most common localization is the thoracic part of the spinal column (70%) [1, 7]. Pain, pathological fractures and neurological deficiencies are the main symptoms caused by the growing tumour mass. Pain is the most common sign, affecting almost 90% of patients, while motor or sensory dysfunctions are observed in 35–75% of cases at the time of diagnosis [1, 7, 8]. Early detection and appropriate treatment is crucial in minimizing the consequences of imminent disability. Median survival in patients with metastatic spread to the spinal column is usually estimated on average as 7 months [1, 8]. The short life expectancy in these patients explains the widespread provision of palliative treatment instead of radical therapy [1, 2].

In selected cases of oligometastatic disease however, radical treatment of a metastatic lesion can result in long-term survival, which implies a search for both efficient methods of identification of patients with long life expectancy and effective methods of treatment. These lesions are often surgically inaccessible and respond poorly to chemotherapy, which is especially true in the case of bone metastases. The modern approach in the management of vertebral metastases complies with structural integrity of the involved spine, the patient’s general condition and individual prognosis [3]. Conventional radiotherapy (RT) of vertebral metastases, first conducted in the 1950s, is regarded as a gold standard in treatment of painful vertebral metastases [1]. Commonly used schedules – 8 Gy in 1 fraction, 20 Gy in 5 fractions and 30 Gy in 10 fractions – are considered equivalent, and their application results in a similar percentage of surviving patients, satisfactory pain control, and diminished risk of pathological fractures and spinal cord compression [1, 9, 10]. Nevertheless, low irradiation doses reduce the probability of satisfactory local control [1, 9, 10]. The median pain response is most often short,
with the reported range of duration of 3–6 months [11]. The main factor limiting the use of conventional radiotherapy in treatment of spinal metastases is localization in the immediate proximity of the spinal cord. Radiation-induced injury may manifest as myelopathy and acute spinal cord oedema. Radiotherapy of multiple vertebral metastases requires application of doses exceeding the dose of tolerance for the spinal cord; therefore suboptimal treatment is executed [1].

The limitations of conventional irradiation triggered application of stereotactic radiotherapy in patients suffering from various neoplasms, from malignant and benign primary tumours to spinal metastases [1, 3, 11–39]. This technique provides precise distribution of a high dose of radiation in 1 to 5 fractions. A steep dose gradient allows for protection of surrounding radiosensitive normal structures (minimizing acute and late toxicities of treatment). Furthermore, stereotactic radiosurgery (SRS) is usually performed in an out-patient fashion. This contributes to reducing the costs of the treatment and improvement of general comfort of patients and their families. Many studies have documented the CyberKnife (CK) system’s ability for protection of surrounding radiosensitive normal structures. Before the SRS procedure, high resolution MRI and CT scans were performed in every patient. Data from imaging

### Table 1. Patient characteristics

| Age | median range |
|-----|--------------|
| 60  | 30–84        |

| Sex |        |
|-----|--------|
| female | 10  |
| male   | 18    |

| Zubrod performance status | 0 | 1 | 2 | 3–4 | 0 |
|---------------------------|---|---|---|-----|---|
|                           | 11| 15| 2  |     | 0 |

| Primary tumour | prostate | breast | lung | medullary thyroid carcinoma | others |
|----------------|----------|--------|------|-----------------------------|--------|
|                | 10       | 6      | 5    | 2                           | 5      |

| Metastases apart from spinal column | present | absent |
|-------------------------------------|---------|--------|
|                                     | 12      | 16     |

| Pain at qualification | present | absent |
|-----------------------|---------|--------|
|                       | 11      | 17     |

| Neurologic signs | present | absent |
|------------------|---------|--------|
|                  | 1       | 27     |

| Decompressive surgery | yes | no |
|-----------------------|-----|----|
|                       | 1   | 27 |

| Chemotherapy | yes | no |
|--------------|-----|----|
|              | 1   | 27 |

| Hormone therapy for breast cancer | yes | no |
|-----------------------------------|-----|----|
|                                    | 4   | 2  |

| Hormone therapy for prostate cancer | yes | no |
|-------------------------------------|-----|----|
|                                     | 9   | 1  |

| Spinal metastatic lesions | isolated | multiple |
|---------------------------|----------|----------|
|                           | 20       | 8        |

| Localization | cervical spine | thoracic spine | lumbar spine | sacrum |
|--------------|----------------|----------------|--------------|--------|
|              | 2              | 17             | 13            | 2      |
studies were transferred to the treatment planning system where target volumes and critical organs were outlined. In every case the Xsight Spine system was used to track the target volume. The applied doses ranged from 8 to 40 Gy (median 16 Gy) in 1–4 fractions (median 2) of 8–15 Gy. Reference isodose was 75–89% (median 80%). Estimated treatment time per fraction ranged from 33 to 101 minutes (mean 56 minutes). A sample treatment plan with pre- and post-radiosurgery imaging data is shown in Figure 1.

Data analysis

Medical records were analyzed to assess pain control and radiological response to the treatment. In prostate cancer patients the biochemical response was also assessed by analysis of PSA levels before and after the treatment. Progression-free survival and overall survival were calculated with the Kaplan-Meier method.

Results

Clinical examination that appraised efficacy of the radiosurgery was performed in 25 cases. Remaining patients were not able to complete scheduled visits or preferred further treatment in centres near their place of residence. Pain as the main initial complaint in the evaluated population was confirmed in 11 cases. Neurological deficits were described in 1 case. In most cases the patients were free from clinical symptoms of metastatic tumour.

General status was assessed with the Zubrod scale. Almost all patients were in very good or good general condition (Zubrod 0 in 11 cases and Zubrod 1 in 15 cases). In only 2 patients the general status was described as satisfactory (Zubrod 2).

Pain control and neurological deficits

The first scheduled visit was conducted a mean of 4.5 months (median 2 months) after SRS. From the group of 11 suffering from vertebral pain before SRS, 8 patients attended the first control visit. Pain was stable in 5 cases (5/8; 62.5%). Three patients reported improvement (3/8; 37.5%). The final follow-up examination was performed a mean of 11 months after radiosurgical treatment. Six patients from the group of 11 with spinal pain before SRS were assessed. Ailments were stable in 3 cases (3/6; 50%) and another 3 patients reported improvement (3/6; 50%). Progression, defined as the occurrence of pain in patients previously free from any complaints, was noted in 4 cases. The remaining patients were free from pain until the last evaluated follow-up visit.

Neurological status was assessed retrospectively by a neurologist, based on written information in medical records. The patient with neurological deficits (lower limb paresis) described before SRS was lost to follow-up. The first follow-up visit revealed deterioration in neurological status (as a consequence of progression of the metastatic spread) in 4 patients (disturbances in skin sensation and lower limb paresis). Decline was transient in 1 case (foot paresis). In 2 cases of lower limb paresis, ailments were present in the final assessment. One patient did not attend the scheduled visit.

After SRS treatment, pharmacotherapy with bisphosphonates was continued in 3 cases (data were not available for 2 patients unable to attend the follow-up visit). In another 4 patients, bisphosphonates were newly applied after SRS completion.
Prostate-specific antigen level  

After CK treatment, PSA levels were quantified during the first and last control. Mean and median values were 51 ng/ml and 7.5 ng/ml (first visit) and 489.4 ng/ml and 19.5 ng/ml (last visit), respectively. After SRS, 7 patients continued hormone therapy, and hormonal treatment was replaced with a different scheme in 6 patients. In 1 case testicular irradiation was conducted, and in 1 case hormone therapy was discontinued.

Local control  

In 17 patients imaging studies were conducted to assess the efficacy of SRS treatment at a mean of 11 months after SRS (final follow-up visit). In 11 cases stabilization was confirmed. Regression was described in 4 patients (figure 2). In 2 patients progression was diagnosed.

Adjuvant and salvage treatment after stereotactic radiosurgery  

Hormonal treatment was continued in 7 of 9 patients with prostate cancer and 3 of 4 patients with breast cancer. Nine patients were qualified for palliative chemotherapy. Three received palliative radiotherapy (localization different than primary treated lesions). Only 1 patient was re-irradiated using stereotactic radiotherapy (CK) at 9 months after SRS (the same lesion). Three patients received additional surgical treatment after SRS (vertebroplasty in 1, laminectomy in 1, and total excision of paraspinal tumour in 1 case).

Overall survival and general condition  

Median overall survival was 20.6 months. Median progression-free survival in patients who attended the follow-up was 12.6 months. General condition did not deteriorate in 12/21 (57%). Eight patients were evaluated below the previous value on the Zubrod scale (8/21; 38%). In 1 case an improvement was observed (5%).

Side effects  

No side effects were observed in our study. There were no cases of acute or late toxicities in the investigated population. Early tolerance of the spinal cord was satisfactory, and no case of acute spinal oedema was detected. No case of acute post-irradiation damage of the adjacent structures (laryngitis, oesophagitis or diarrhoea) was noted, either. Similarly, there was no case of remote toxicities. Deterioration in neurological status diagnosed in 4 patients was a result of ongoing metastatic spread or local progression.

Discussion  

According to the meta-analysis by Sohn et al., the number of studies and the quality of available literature on spinal metastases are generally low or very low [15]. There are only two randomized controlled studies on radiosurgical treatment of spinal metastases, and only one investigation has been closed and published to date [11, 16]. The majority of the available literature represents retrospective studies analyzing outcomes of SRS in populations from 20 to 1075 patients [1, 3, 15, 17–24].

Pain control and neurological improvement  

In our evaluation, pain control was satisfactory in all patients who attended scheduled control visits (stable in 62.5% and 50% in the first and last assessment; improvement in 37.5% and 50% at the first and last visit; respectively). The deterioration in neurological status observed in our population was a consequence of progression of the disease.

Outcomes similar to ours have been presented in the literature. Ryu et al. described complete pain relief in 46%, partial relief in 18.9%, and stable symptoms in 16.2% at 8 weeks after SRS completion. The overall 1-year pain control rate was 84%. Significant improvement in neurological function was confirmed in 40% of patients at 1 week after SRS [17]. Likewise, Gerszten et al. observed long-term satisfactory pain control in 86% of patients in median follow-up of 21 months. Neurological status improved in 85% of cases [24]. Furthermore, Gibbs et al. confirmed a decrease in pain and neurological symptoms in 84% of...
patients after SRS [15]. Nikolajek et al. described improvement in pain control in 75% of patients (all received SRS after previous conventionally fractionated radiotherapy) and progression of neurological symptoms in 12.9% [22]. Gagnon et al. described a decrease of pain within 1 week for most patients and total pain reduction in 38% at the end of the month after SRS [27]. Similarly, in the analysis by Wowra et al., most patients experienced significant pain relief in a follow-up period of 1.4 years. Pain recurrence was observed in 3 (6%) patients [28]. Finally, Wang et al. reported significant pain improvement and reduction in opioid use in most patients during 6 months after stereotactic body radiation therapy (SBRT) (52.9% did not experience any pain), as well [16].

Local control and overall survival

Local control in patients receiving SRS is usually estimated at about 90% [3, 15, 24]. Our outcome with 88.2% of local control at a mean of 11 months after SRS is in line with the available literature. The median overall survival of 20.6 months and median progression-free survival of 12.6 months are similar to the results of other studies, as well.

Degen et al. confirmed 95% local control in the mean follow-up of 350 days [32]. Similarly, Chang et al. reported a 1-year 84% progression-free survival [30]. According to Gill’s evaluation, local control in 1 year and in 2 years were 80% and 73%, respectively. The overall survival rate was 80 and 57% in 1 year and in 2 years, respectively [3]. Furthermore, Ryu et al. reported the 1-year survival rate as 74.3% [17]. Nikolajek et al. confirmed 12.9% of local failures. The actuarial rates of freedom from local failure at 6/12/18 months were 93%/88%/85%, respectively. Median overall survival was 16.2 months after SRS [22]. According to Gerszten et al. and Yamada et al., satisfactory control was achieved in 90% of patients [25, 26]. Finally, Wang et al. estimated actuarial tumour progression-free survival rates of 80.5% and 72.4% at 1 year and 2 years after SBRT, respectively. The median overall survival time was 23 months after SBRT, and 1-year and 2-year actuarial survival rates were 71.9% and 48.8%, respectively [16].

Doses and fractionation schedules

Dose prescription is determined based on primary tumour histopathology and spinal cord tolerance [15]. Single fraction SRS doses usually range from 8 to 24 Gy. There are numerous hypofractionation schedules, e.g.: 4 Gy × 5 fractions, 6 Gy × 5 fractions, 8 Gy × 3 fractions or 9 Gy × 3 fractions [15]. In our evaluation the mean applied dose was 16.8 Gy (range 8–40 Gy), delivered in 1–4 fractions of mean 8.7 Gy (range 4–15 Gy). This dose range is similar to that reported by other authors commonly applying 10 Gy to 30 Gy in 1 to 5 fractions [3, 14–18, 23–28]. An important issue is also the time needed to deliver a single fraction. Due to their complexity and numerous beams used, CyberKnife plans require long irradiation times [29]. In the current study it ranged from half an hour to one and a half hours per fraction. Such a long delivery time is not suitable for patients in poor general condition. Consequently, this kind of treatment should be offered to patients in good general status and with a long expected time of survival, preferentially to patients with single metastases and a controlled primary, which could give a chance of a cure.

Complications

Stereotactic radiosurgery is considered as a safe treatment option. The reported complications of spinal radiosurgery include: oesophagitis, dysphagia, diarrhoea, parasthesia, laryngitis, compression fracture and transient radiculitis [15, 30–35]. Radiation-induced spinal cord injury is an extremely rare complication [15]. Our evaluation did not reveal any early and/or late complications of SRS treatment. Similarly, many authors did not report any complications [3, 15, 17, 27, 28]. Nikolajek et al. documented 1 case of progressive paraparesis. Apart from that, no other toxicities have been observed [22]. Gibbs and colleagues described 3 cases and subsequently 6 cases of spinal cord injuries in their studies [18, 23]. However, Wang et al. [16] described 12 cases of non-neurological grade 3 toxicities (nausea, vomiting, diarrhoea, fatigue, dysphagia, neck pain, diaphoresis, pain associated with severe tongue oedema and trismus, non-cardiac chest pain). No radiation-induced myelopathy occurred. Against the background of the cited papers, the treatment tolerance in our series is excellent; the patients are however still being followed up whenever possible in order not to miss possible late complications.

Hormonal status

In our study, radiosurgical treatment did not change the PSA level significantly in the early period after SRS. The later elevation of the PSA levels can be attributed to progression in unirradiated sites (all but 1 patient with increasing PSA levels had other metastases) rather than to local failure in the irradiated area. According to available literature, application of CK radiosurgery may cause a decrease of PSA level [36–39]. In contrast to some other studies, in our investigation a large subset of patients was receiving hormone therapy for many weeks or months preceding SRS. Moreover, many patients required modification of hormonal treatment after SRS. Thus, precise and reliable determination of dependence between PSA level fluctuations and CK radiosurgery timing and dose is hampered in our patients.

In conclusion, robotic stereotactic radiosurgery, as a part of multimodality therapy for spinal tumours, is safe and effective. Because of long treatment times, patients in good general status should be selected for this kind of treatment, preferentially without signs of active disease outside the treated area.

The authors declare no conflict of interest.

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