Physica Medica 64 (2019) 311–316

Contents lists available at ScienceDirect

Physica Medica

journal homepage: www.elsevier.com/locate/ejmp

Original paper

Re-irradiation of vertebral bodies

Dorota Gabryś

Radiotherapy Department, Maria Sklodowska - Curie Memorial Cancer Center and Institute of Oncology Gliwice Branch, Wybrzeze Armii Krajowej 15, 44-101 Gliwice, Poland

ARTICLE INFO

Keywords:
Complications
Vertebral body
Radiotherapy
Re-irradiation
Tissue tolerance

ABSTRACT

Improvements in clinical care and therapy mean that more patients are diagnosed and living longer with vertebral metastases. Thus, they are at risk of the development of recurrence that requires re-irradiation. Normal tissues often recover some of the damage caused by the primary radiotherapy with time and specific normal tissues can tolerate a considerable retreatment radiation dose. However, the risk of normal tissue damage and the impact on the quality of life must be considered and should be done with maximum care and accuracy especially in the vertebral area.

For many years conventional external beam radiation therapy was the standard treatment modality. Fortunately, with crucial technological progress in the field of radiation oncology we are able to integrate body imaging with accurate treatment delivery methods as stereotactic body radiotherapy to improve the efficacy, shorten the overall treatment time and potentially reduce treatment-related toxicities.

A short description of re-irradiation strategy covering diagnostic procedures, volume delineation, dose reconstructions, treatment planning, and guidelines are outlined. Moreover, publications on vertebral bodies re-irradiation summarizing available knowledge about toxicity, dose-volume constraints, local control, and pain response are followed.

Although the knowledge is limited to a series of a single institution, it shows that re-irradiation is an effective treatment for local control and pain response. Furthermore, treatment was also shown to be safe with low risk of spinal cord damage which is one of the most worrisome toxicity.

1. Introduction

Recurrence or second cancers regularly require a second (or third) radio-oncological treatment. Fortunately, the amount and quality of clinical data on the outcome and particularly the adverse events of re-irradiation constantly ameliorate [1,2]. Due to improvements in clinical care and therapy, more and more patients are being diagnosed with and living longer with vertebral metastases. Approximately 60–70% of patients with systemic cancer will develop vertebral metastases [3]. Vertebral tumours are important in clinical practice because their presence can significantly affect patient quality of life. In respect to their localisation (bone, epidural space, leptomeninges or spinal cord) they can express variable clinical presentation. In the majority of cases, it is pain, fracture, mechanical instability, radiculopathy, spinal cord compression, and neurological dysfunctions. The effectiveness of 3D conformal external beam radiotherapy (cEBRT) has been limited to complete pain response rates of less than 20% and a partial response of 60% [4]. Furthermore, 20% of patients treated with low dose cEBRT eg. 8 Gy in 1 fraction will require re-irradiation due to pain progression within months of the first course [5]. Therefore, there is a need to improve the outcome in this group of patients. Moreover, patients with longer survival will develop not only pain progression but also tumour progression and subsequently need re-irradiation.

In the recurrent condition, for a successful salvage safe radiation dose distribution is needed and a wide range of techniques and methods of dose fractionation makes it possible to choose a such 3D technique that concentrates the radiation beam in the target volume (GTV – gross tumour volume, CTV – clinical target volume, PTV – planning target volume) with a rapid dose gradient outside of it, i.e. in the volume of adjacent healthy tissues/organs. However, in clinical practice the choice of the appropriate total dose is a form of compromise between a chance of curing the tumour and a risk of serious, late radiation complications in healthy tissues. While the chance of curing at the presence of complete regression can be reliably estimated based on regular patient observation after treatment, the serious radiation reactions in healthy tissues/organs manifest themselves late, sometimes many years after irradiation and the risk of their disclosure is generally assumed and estimated based on accumulated empirical knowledge. The increase of such a risk over time reduces the expected therapeutic profit and the rate of cures achieved without complications decreases. That is

E-mail address: Dorota.Gabrys@io.gliwice.pl.

https://doi.org/10.1016/j.ejmp.2019.07.023
Received 31 January 2019; Received in revised form 30 May 2019; Accepted 26 July 2019
Available online 02 August 2019

why the years of research on the mechanisms of late post-radiation reactions in healthy organs are so important in order to make continuous alleged estimation of the risk of such complications.

Although, with increasing clinical experience and the number of publications our knowledge of the normal tissue recovery from prior radiotherapy is incomplete but growing. In addition, the benefits of re-irradiation in the vertebral area are increasingly appreciated. Therefore, the intent of the current review is to discuss the role of re-irradiation in the treatment of vertebral body metastases within the scope of available published evidence. This overview aims to provide a short description of re-irradiation strategy covering diagnostic procedures, volume delineation, dose reconstructions, treatment planning and available guidelines.

2. Diagnostic procedures

We can use variable imaging modalities to diagnose the patient and visualise tumour volume. The fastest accessibility is computed tomography (CT). CT enables to asses osseous integrity, cortical destruction and tumour matrix. The disadvantage of CT is difficulty with the cortical destruction detection when osteoporosis or degenerative changes occur [3,6]. Opposite to CT, magnetic resonance (MR) is better at assessing soft tissue involvement, enables differentiation between normal and pathologic tissues, allows for earlier detection of pathology [7,8]. Moreover, MR allows description of solid and cystic components, and assessment of edema, as well as involvement of the epidural space, cord compression, and cord signal abnormality [7]. MR is the only imaging technique that allows direct visualization of bone marrow and its components with high spatial resolution. The MR sequences combinations are useful for the detection of bone marrow abnormalities and are able to discriminate benign from malignant bone marrow changes [3,9]. If there is a contraindication to MR imaging, CT myelography can help in evaluation of cord compression, and intradural disease [7]. It may be necessary to use positron emission tomography (PET). [18F] FDG PET/CT highlights the increased glucose metabolism in tumour cells, allowing for early detection of marrow involvement, as well as assessment of treatment response [7].

For target and organ-at-risk delineation MR images should be used; typically, the T1 sequence is the sequence of choice because both the spinal cord and tumour within the bone are visualised. Additionally, T2 image can help with spinal cord and paraspinal/epidural disease delineation. For accurate volume delineation, both CT and MR are essential because CT provides the information with respect to disease within the bone itself and characterisation of lytic versus blastic versus mixed lesion [10]. Moreover, MR is thought to better differentiate between metastatic compression and vertebral fractures after primary radiotherapy. Metastatic bone disease are divided into two main categories osteoblastic and osteolytic. Prostate cancer, carcinoid, and other endocrine tumors are forming osteoblastic lesions, and osteolytic lesions are more frequently observed in breast, lung, and kidney tumors. However, most types of cancer show a broad spectrum between these two extremes and mixed changes appear [3,10,11]. [^{18}F]-FDG PET is more sensitive for detection of osteolytic metastasis than osteoblastic metastasis. Furthermore [^{18}F]-FDG PET was shown to differentiate between osteoporotic and malignant vertebral compression fractures rev. [3].

3. Conventional radiotherapy

Vertebral bodies cEBRT was possible even with older irradiation techniques, but the traditional intent of cEBRT has been strictly palliative, with various low dose cEBRT balancing toxicity and improvement in patient complaint. Typically posterior-anterior (PA) or lateral fields were used to irradiate vertebral bodies. With the introduction of multi-leaf collimator (MLC) fields area was reduced. Unfortunately, such therapy does not give a satisfactory result as it was shown in the recent prospective study on patients re-irradiated for bone metastases also for vertebral bodies [12]. In this work variable primary doses were used. Patients were divided into 8 Gy in a single fraction or 20 Gy in multiple fractions groups. An intention to treat analysis revealed disappointing results, with an overall pain response of around 30% and a complete pain response only in 8% of patients. Doses used were relatively low and only patients were ineligible if they had clinical or radiological evidence of spinal cord compression, a pathological fracture, or an impending fracture that needed to be fixed surgically. Moreover, pain response was evaluated at short - 2 month follow up. Therefore, there is a need for innovative therapeutic strategies to improve outcomes.

4. Radiosurgery

Enormous technological progress has been made in the field of radiation oncology in software as well as in hardware. Technical innovations as three even four-dimensional body imaging allow us to precise and repeated patients irradiation. This in turn with improved oncological treatment and care prolonged patients survival even in the presence of metastatic disease. One such innovation is stereotactic body radiotherapy (SBRT), which allows for tumour dose escalation with precise delivery of accurate radiotherapy while differentially dosing the non-target tissues, especially spinal cord to a lower and tolerable dose. This is very important during re-irradiation when we are dealing with the increased possibility of side effects.

To the unquestionable benefits of SBRT we can include fewer fractions and shorter treatment time. Such a treatment is more convenient for patients especially in poor performance status and when people live far away from a radiotherapy center. It is not well known whether a single high dose of radiosurgery possesses a different mechanism of cell kills than 3D conformal radiotherapy [13]. However, there is some evidence that higher doses are potentially more effective because when a dose per fraction is higher than 10 Gy radiation directly kills tumour cells but also causes significant damage in tumor vasculature [14,15]. Moreover, increased release of tumor-associated antigens and proinflammatory cytokines, caused by direct tumour irradiation and vascular damage, initiates an immune response against a tumour [16–18]. Image-guided spine radiosurgery is possible and applicable because vertebra has good visibility on X-ray image verification or cone beam computed tomography (CBCT). This together with accurate immobilization and patient positioning minimize possible mistakes. High precision of SBRT may lead to less normal tissue irradiation, but on the other hand, small margins without accurate positioning create a possibility of unacceptable errors leading to an overdose of the normal tissue and underdose of tumour. Therefore repeated radiotherapy within vertebral body should be performed with care and accuracy with detailed case by case diagnostic procedures, qualification, treatment planning, treatment delivery and follow up.

5. Decision framework

During re-irradiation of the vertebral body one come across with various situations as in-field failure which refers to tumor regrowth inside the target volume. Such a failure may be caused by low radiosurgical dose or radioresistant tumor. Marginal failure is within the volume of rapid dose drop off outside of the target volume which may be related to the geographical miss or patient set up error, or underestimation of the target volume. Finally, one could have a patient with a new tumour within untreated vertebra due to the progression of metastatic disease [13]. Depending on specific situation careful decision about treatment should be taken.

Decision-making process in vertebral metastases over the past decade has evolved from simple choices regarding the need for either surgery or cEBRT to complex multimodality assessments that require the integration of new technologies such as SBRT, less or more

aggressive surgical procedures but also chemotherapy, hormones, immunotherapy, or biologics. They correspond to primary radiotherapy but could be also incorporated during re-irradiation qualification. There is modern framework which can be used for accurate patient qualification for dedicated treatment of metastatic vertebral tumors. The NOMS integrates multimodality therapy to optimize local tumor control, pain relief, and restoration or preservation of neurologic function as well as minimizes morbidity especially in systemically ill metastatic patients. NOMS decision framework consists of four considerations published before [19]. The neurologic consideration is an assessment of the degree of epidural spinal cord compression, myelopathy, and/or functional radiculopathy. Radiologic criteria allow us to estimate the advancement of tumour within the vertebral body. For this, one can use a six-point grading system describing the degree of ESCC which was designed and validated by the SOSG. The system uses axial T2-weighted images at the site of most severe compression [15,20].

The oncologic consideration is predicated on the expected tumoral response and durability of response to available treatments. It is probably one of the most significant factors in the assessment of tumour response to cEBRT and sustained control. Fortunately, there is also growing evidence suggesting that SBRT could achieve excellent local control regardless traditionally radioresistant tumour histology to cEBRT [21–28].

Mechanical instability is a separate consideration defined for pathologic fractures which needs a surgical intervention. Spinal instability is defined by the Spine Oncology Study Group (SOSG) as the “loss of spinal integrity as a result of a neoplastic process that is associated with movement-related pain, symptomatic or progressive deformity, and/or neural compromise under physiologic loads” [22]. Spinal instability depends on both clinical and radiographic criteria. Clinically, the patient suffers severe movement-related pain that corresponds to damage of the specific spinal level. This pain must be differentiated from biologic pain, which appears in the evenings and mornings and responds to steroids and radiation [19,23]. Mechanical instability can be treated with surgery but radiation or systemic therapy will not stabilize the spine. In the absence of mechanical instability, radiation therapy is considered as a primary treatment option in Grades 0, 1a, and 1b. Higher grades as 2 and 3 which correspond to high grade ESCC require surgical decompression before irradiation unless a tumour is highly radiosensitive [19].

Last but not least the fourth consideration is the extent of systemic disease. We should take into account the patient performance status, medical comorbidities, and advancement of the metastatic disease that can significantly impair the patient tolerance to proposed treatment (especially for the surgical procedure) and the overall expected patient survival.

6. International stereotactic radiosurgery society practice guidelines

The available guidelines dedicated to re-irradiation are very limited in detailed informations. It is recommended that after primary cEBRT, and SBRT retreatment with SBRT should be taken into account as a therapeutic option in suitable patients (level of evidence III). In patients with clinical features concerning for malignant epidural spinal compression, mechanical instability, or baseline vertebral body compression, fracture, a spine surgeon should assess the patient before re-irradiation (level of evidence II) [5].

7. Questions before re-irradiation

If we decide that patient is a candidate for re-irradiation upfront we have to answer additional questions. We need to know exactly which part of vertebra we will irradiate and what kind of toxicity we already have? We expect different toxicity profile eg. in cervical and lumbar part of the vertebral body. The important question is what kind of toxicity we expect after our secondary treatment, do the structures which were irradiated are already damaged, does patient already have evident dysfunction and complication or did not have any problems during and after primary treatment? Moreover, especially in vertebra region time between courses is crucial for possible re-irradiation especially in term of spinal cord toxicity. Next, we need to have information about primary total delivered dose and dose per fraction [2]. Finally, what we can achieve with re-irradiation, remembering the sentence said by Hippocrates “Primum non nocere”.

8. Volume delineation in vertebral radiosurgery

Unfortunately, we do not have delineation guidelines for re-irradiation of vertebral bodies. All published reports on this topic in a limited way describe the GTV and PTV delineation method rev. [5,10]. We can use guidelines for stereotactic radiotherapy published in 2012, although they are not intended to be rigid guidelines and should not replace clinical experience or judgment [29]. It is suggested to use the modified system that divides each vertebral body into 6 sectors and accordingly to include a bony CTV margin including abnormal bone marrow signal suspicious for microscopic invasion adjacent to the gross tumor in the CTV. Generally, the entire vertebral body, pedicle, transverse process, lamina, or spinous process should be included in the CTV if any part of these regions contained the GTV. Moreover, irradiation of the whole vertebra should be avoided, what can limit the volume of the CTV and can help in treatment planning to decrease the volume of normal structures. CTV expansion should encompass adjacent physiologic appearing bone marrow spaces due to the potential of subclinical disease which can be the place of recurrence [30]. Additional ≤ 3 mm might be added to create PTV. As authors summarised this recommendation focuses on common situations when vertebral radiotherapy is used as primary treatment and cannot necessarily be applied to the re-irradiation or postoperative clinical settings. Re-irradiation target volumes should be delineated on the particular patient base taking into account the individual clinical situation. Volumes should be limited as much as possible to decrease the toxicity risk but without compromising the treatment outcome. If possible, the guidelines described above should be applied but in specific situation eg. in locally advanced cases in previously irradiated volume only tumour delineation could be performed without CTV contouring and PTV can be created as additional ≤ 3 mm to GTV.

9. Dose constraints

If we use only information from dose volume histograms (DVH) of separate plans then we do not have the exact information about combined dose. The best situation is when both primary and re-irradiation was performed in the same center and we can co-register the treatment plans using specific programs. Commercial softwares are a treatment planning evaluation systems, by which we can integrate imaging scans and treatments information from a particular patient. Therefore, a combined dose can be associated with images for review of treatment plans using isodose curves and DVH. The problem is when a patient was irradiated in the other center and treatment plans are not available. Then one should ask the original center for treatment plans, which can be imported to system and co-registered. Unfortunately, in the worst case scenario when there are no available previous treatment plans for co-registration, one should adopt the most unfavourable (the highest) dose within normal critical tissues. In particular the spinal cord in respect to the previously prescribed dose or if possible the maximum dose from previous DVH.

A possibility of plan co-registration with accurate delineation of the critical structures and strict adherence to safe dose limits is very important as seen in this case of patient treated for metastatic rectal cancer after several lines of chemotherapy with multiple metastatic disease. An example of combined radiation doses from three separate

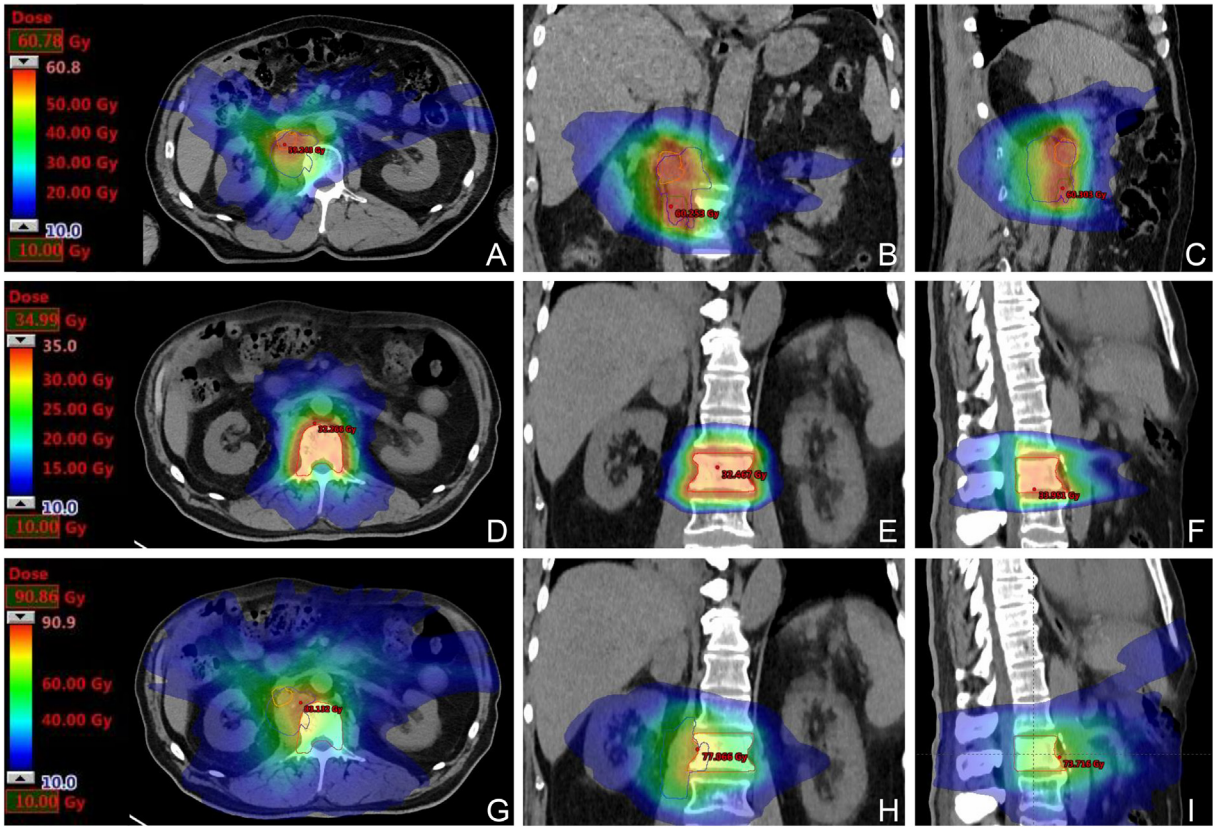

Fig. 1. Example of multiple radiotherapy for vertebral body. Threshold colour wash dose is set to 10 Gy. A – axial view, B – coronal view, C – sagittal view show combined radiation dose distribution overlaying CT images of a patient treated twice with CyberKnife™, both times 30 Gy/3 fractions. First radiotherapy GTV (blue), second radiotherapy GTV (orange and green). D – axial view, E – coronal view, F – sagittal view show radiation dose distribution overlaying CT of third radiotherapy delivered with VMAT to the total dose 30 Gy/10 fractions. Third radiotherapy GTV (red). G – axial view, H – coronal view, I – sagittal view show combined radiation doses across GTVs and normal tissue anatomy delivered with three separate plans twice on CyberKnife™ and once on True Beam™. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

treatment plans is shown on Fig. 1. Patient was suffering from uncontrolled pain from vertebral body which do not allowed him to sleep in vertical position even with the use of several painkillers. After the first radiotherapy he reported significant increase in pain control and improvement in sleeping. Meanwhile, he underwent irradiation to lung and liver metastases. Five months later there was a progression of tumour mass together with pain grade increase and patient underwent second radiotherapy with stabilization of pain symptoms and stabilization of tumour volume. Unfortunately, 7 months later the patient presented with tumour progression within vertebral body. The patient was irradiated for the third time with minimal complaints response.

The vertebral column extends throughout the whole body, therefore variable critical structures are located in their vicinity depending on the level and have to be taken into account during the treatment planning. The most crucial during re-irradiation is the spinal cord because its damage can significantly deteriorate the patient's quality of life. There is clear evidence for substantial long-term recovery, indicating that retreatment is feasible, although the degree depends on the time interval from the initial irradiation exposure [1]. For the estimation of the re-irradiation tolerance for spinal cord, the initial tolerance must be defined. Therefore, in order to assess the accurate dose comparison a spinal cord dose normalized to EQD2 is used, assuming an α/β of 2. Both human and primate data demonstrate that at an EQD2 of 55 Gy, the incidence of myelopathy is < 3% [2,31,32]. At a dose of 60 Gy, the incidence of myelopathy is about 5% for doses per fraction < 2.5 Gy and for one fraction per day. This level of risk may be acceptable in a re-irradiation situation, which is frequently the last curative option for the patient. However, the dose to the spinal cord is usually less than the dose to the PTV, which must be included in the calculation of the initial dose. Based on these considerations, re-irradiation with curative intent is often possible [2]. As time between the initial irradiation and re-treatment plays an important role. It was shown that if the interval between the two radiotherapy courses was longer than 6 months, and the EQD2 in each course was 48 Gy, the risk for myelopathy was low after a total EQD2 of 68 Gy [33]. Morbidity induced by re-irradiation may manifest earlier than after single irradiation. The mean latent time before clinical symptoms after a single course of radiotherapy (EQD2 60.5 Gy) was 18.5 months. After re-irradiation to a total EQD2 of 74 Gy, myelopathies were observed after a significantly shorter mean latent time of 11.4 months [34].

Relatively low rates of radiation myelopathies are found in re-irradiation setting what might be related to the small number of patients who underwent re-irradiation to high dose delivered to the spinal cord (in substantial number of centers, “safe” dose constraints are used), short overall survival, fact that the maximum dose delivered to the spinal cord during re-irradiation usually do not overlap with the maximum dose delivered to the spinal cord of first treatment. This may be related not only to the inter- and intrafractional organ motion but also to the variable body changes as body weight gain or loss. Moreover better accuracy of treatment delivery allows reducing the dose within these critical structures.

The evidence-based data on doses come from retrospective study, assessed detailed dosimetric data using the thecal sac (covers of the spinal canal that is filled with cerebrospinal fluid) as the surrogate for the true cord in patients who either did or did not develop radiation myelopathy after receiving salvage SBRT following initial cEBRT [35]. Contouring the thecal sac, allows for a small anatomic margin (typically, 1.5 mm) for uncertainty in spinal cord contour delineation, inter-

and intrafraction positional variation, and organ motion (on average within 0.5 mm) [36,37]. The authors concluded that SBRT after an interval of at least 5 months after cEBRT, a re-irradiation SBRT maximum point EQD2 to the thecal sac of 25 Gy and a total thecal sac maximum point EQD2 of 70 Gy is clinically safe [35].

The spinal cord is considered a serial organ which partial damage will cause malfunction. Nevertheless, various recent data suggest that a volume dependency for spinal cord irradiation might exist. Animal studies confirmed safety of small volume irradiation up to higher doses without neurological consequences [38,39]. Although limited there is evidence from patients studies indicating that high spinal cord doses within a minimal volume, during re-irradiation may be applied. Especially using topographically different high point doses, together with treatment and tumour associated risks [40,41]. It is necessary to further collect clinical data on the effect of the dose on the spinal cord in order to confirm long term re-irradiation safety and create applicable dose constraints. Moreover, it is important to conduct prospective studies with dose escalation within target volume as well as within surrounding critical structures. There are various attempts to predict the increase in tolerance of spinal cord with time, using conservative parameters. Alternative models for estimating the radiotherapy retreatment dose for the spinal cord were published [42,43].

10. Clinical outcome

The current evidence is limited to a single institution retrospective series with few prospective data with respect to re-irradiation in the salvage setting. Moreover, studies are limited by the low number of patients, relatively short follow up and the mixture of primary and metastatic status besides vertebrae rev. [10]. The authors concluded that despite significant variability in terms of treatment planning, delivery method, dose/fractionation, and symptom assessment, SBRT seems to provide significant and durable local control and symptom management. As a primary treatment in the majority of cases, cEBRT was applied with dose ranged from 30 Gy/10 fractions to 40 Gy/20 fractions. The re-irradiation was performed using SBRT dose ranged from 16 Gy/one fraction to 30 Gy/five fractions rev. [10]. An optimal fractionation schedule for spine SBRT is not defined, with both single and multiple fraction regimens are commonly used. Fractionation allows using intrinsic differences in radiosensitivity between a tumour and spinal cord. What in turn allow to deliver higher doses to the epidural space - place of common recurrences after cEBRT [44]. Median 1 year local control rates ranged from 66 to 90% and pain response from 65 to 81%, higher than after cEBRT re-irradiation. Due to the character of patients, which usually poses a multi metastatic disease overall survival is modest rev. [10].

The risk of major adverse events as radiation myelopathy is low, with the most common adverse event being vertebral compression fracture (VCF) more often seen after single fraction SBRT in comparison to fractionated radiotherapy rev. [10,45]. Careful consideration should be given to response assessment after re-irradiation, as osteoradionecrosis, fibrosis, or VCF can be mistaken for local progression. Therefore, the biopsy may be considered where local progression is suspected after SBRT [45]. On the other hand recent report on symptomatic re-irradiated patients with progression of pain, neurological symptoms, and VCF who underwent salvage surgery shown that when correlating the histopathological findings and clinical symptoms with radiological findings most specimens from patients with a progressive tumour on imaging contain a viable and proliferative tumour [46]. This suggests that MR could be a reliable tool for the detection of tumour progression. Furthermore, the incidence of osteonecrosis and soft tissue necrosis was not increased in specimens from patients with pathological fractures but bone marrow fibrosis was increased. Increased fibrosis might be related to changes induced by radiation in connective tissue that is visible in bone as well [46].

11. Follow up

Follow up protocols varied between studies. In many cases they were not specifically discussed. If the information is given CT scan or MR follow up is recommended. Usually, it is suggested to perform imaging every 3–4 months. Definition of local failure varied from radiographic in-field progression to radiographic and/or clinical progression rev. [5].

12. Conclusion

Although the knowledge is limited to a series of a single institution, it was shown that re-irradiation is an effective treatment for local control and pain response. Furthermore, treatment was also shown to be safe with low risk of spinal cord damage which is one of the most worrisome toxicity.

Declaration of Competing Interest

The authors state no conflict of interest.

Acknowledgements

I would like to thank Andrzej Wojcik, Iuliana Toma-Dasu, Lovisa Lundholm and Mattias Hedman for organizing a Workshop: Current challenges of patient re-irradiation which was the reason for this publication.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmp.2019.07.023.

References

[1] Dorr W, Gabrys D. The principles and practice of re-irradiation in clinical oncology: an overview. Clin Oncol (R Coll Radiol) 2018;30(2):67–72.
[2] Joiner M, van der Kogel A. Basic Clinical Radiobiology (chapter 14, 23). 5th ed. CRC Press; 2018. August.
[3] Shah LM, Salzman KL. Imaging of Spinal Metastatic Disease. Int J Surg Oncol 2011;2011:1–12.
[4] Chow E, Harris K, Fan G, et al. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol 2007;25(11):1423–36.
[5] Myrehaug S, Sahgal A, Hayashi M, et al. Reirradiation spine stereotactic body radiation therapy for spinal metastases: systematic review. J Neurosurg Spine 2017;27(4):428–35.
[6] Kamholtz R, Sze G. Current imaging in spinal metastatic disease. Semin Oncol 1991;18(2):158–69.
[7] Gibbs WN, Nael K, Doshi AH, et al. Spine oncology: imaging and intervention. Radiol Clin North Am 2019;57(2):377–95.
[8] Norman D, Mills CM, Brant-Zawadzki M, et al. Magnetic resonance imaging of the spinal cord and canal: potentials and limitations. AJR Am J Roentgenol 1983;141(6):1147–52.
[9] Daffner RH, Lupetin AR, Dash N, et al. MRI in the detection of malignant infiltration of bone marrow. AJR Am J Roentgenol 1986;146(2):353–8.
[10] Myrehaug S, Soliman H, Tseng C, et al. Re-irradiation of vertebral body metastases: treatment in the radiosurgery era. Clin Oncol (R Coll Radiol) 2018;30(2):85–92.
[11] Nayir E. Pathogenesis of bone metastasis. J Oncol Sci 2016;1:13–6.
[12] Chow E, van der Linden YM, Roos D, et al. Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial. Lancet Oncol 2014;15(2):164–71.
[13] Ryu S, Yoon H, Stessin A, et al. Contemporary treatment with radiosurgery for spine metastasis and spinal cord compression in 2015. Radiat Oncol J 2015;33(1):1–11.
[14] Song CW, Kim MS, Cho LC, et al. Radiobiological basis of SBRT and SRS. Int J Clin Oncol 2014;19(4):570–8.
[15] Barzilai O, Fisher CG, Bilsky MH. State of the art treatment of spinal metastatic disease. Neurosurgery 2018;82(6):757–69.
[16] Lee Y, Auh SL, Wang Y, et al. Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. Blood 2009;114(3):589–95.
[17] Kaur P, Asea A. Radiation-induced effects and the immune system in cancer. Front Oncol 2012;2:191.
[18] Barzilai O, Laufer I, Yamada Y, et al. Integrating evidence-based medicine for treatment of spinal metastases into a decision framework: neurologic, oncologic, mechanicals stability, and systemic disease. J Clin Oncol 2017;35(21):2419–27.

[19] Laufer I, Rubin DG, Lis E, et al. The NOMS framework: approach to the treatment of spinal metastatic tumors. Oncologist 2013;18(6):744–51.
[20] Bilsky MH, Laufer I, Fourney DR, et al. Reliability analysis of the epidural spinal cord compression scale. J Neurosurg Spine 2010;13(3):324–8.
[21] Gerszten PC, Mendel E, Yamada Y. Radiotherapy and radiosurgery for metastatic spine disease: what are the options, indications, and outcomes? Spine (Phila Pa 1976) 2009;34(22 Suppl):S78–92.
[22] Fisher CG, DiPaola CP, Ryken TC, et al. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine oncology study group. Spine (Phila Pa 1976) 2010;35(22):E1221–9.
[23] Posner JB. Back pain and epidural spinal cord compression. Med Clin North Am 1987;71(2):185–205.
[24] Bilsky MH, Shannon FJ, Sheppard S, et al. Diagnosis and management of a metastatic tumor in the atlantoaxial spine. Spine (Phila Pa1976) 2002;27(10):1062–9.
[25] Bilsky MH, Boakye M, Collignon F, et al. Operative management of metastatic and malignant primary subaxial cervical tumors. J Neurosurg Spine 2005;2(3):256–64.
[26] Burton AW, Mendel E. Vertebroplasty and kyphoplasty. Pain Phys. 2003;6(3):335–41.
[27] Hentschel SJ, Burton AW, Fourney DR, et al. Percutaneous vertebroplasty and kyphoplasty performed at a cancer center: refuting proposed contraindications. J Neurosurg Spine 2005;2(4):436–40.
[28] Ogawa H, Ito K, Shimizuguchi T, et al. Re-irradiation for painful bone metastases using stereotactic body radiotherapy. Acta Oncol 2018;57(12):1700–4.
[29] Cox BW, Spratt DE, Lovelock M, et al. International Spine radiosurgery consortium consensus guidelines for target volume definition in spinal stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 2012;83(5):e597–605.
[30] Chang EL, Shiu AS, Mendel E, et al. Phase I/II study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure. J Neurosurg Spine 2007;7(2):151–60.
[31] Baumann M, Budach V, Appold S. [Radiation tolerance of the human spinal cord]. Strahlenther Onkol 1994;170(3):131–9.
[32] Schultheiss TE. The radiation dose-response of the human spinal cord. Int J Radiat Oncol Biol Phys 2008;71(5):1455–9.
[33] Nieder C, Grosu AL, Andratschke NH, et al. Update of human spinal cord reirradiation tolerance based on additional data from 38 patients. Int J Radiat Oncol Biol Phys 2006;66(5):1446–9.
[34] Wong CS, Van Dyk J, Milosevic M, et al. Radiation myelopathy following single courses of radiotherapy and retreatment. Int J Radiat Oncol Biol Phys 1994;30(3):575–81.
[35] Sahgal A, Ma L, Weinberg V, et al. Reirradiation human spinal cord tolerance for stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 2012;82(1):107–16.
[36] Ma L, Sahgal A, Hossain S, et al. Nonrandom intrafraction target motions and general strategy for correction of spine stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 2009;75(4):1261–5.
[37] Cai J, Sheng K, Sheehan JP, et al. Evaluation of thoracic spinal cord motion using dynamic MRI. Radiother Oncol 2007;84(3):279–82.
[38] van der Kogel AJ. Dose-volume effects in the spinal cord. Radiother Oncol 1993;29(2):105–9.
[39] Medin PM, Foster RD, van der Kogel AJ, et al. Spinal cord tolerance to single-session uniform irradiation in pigs: implications for a dose-volume effect. Radiother Oncol 2013;106(1):101–5.
[40] Zschaeck S, Wust P, Graf R, et al. Spinal cord constraints in the era of high-precision radiotherapy : Retrospective analysis of 62 spinal/paraspinal lesions with possible infringements of spinal cord constraints within a minimal volume. Strahlenther Onkol 2017;193(7):561–9.
[41] Kawashiro S, Harada H, Katagiri H, et al. Reirradiation of spinal metastases with intensity-modulated radiation therapy: an analysis of 23 patients. J Radiat Res 2016;57(2):150–6.
[42] Jones B, Hopewell JW. Alternative models for estimating the radiotherapy retreatment dose for the spinal cord. Int J Radiat Biol 2014;90(9):731–41.
[43] Jones B, Hopewell JW. Spinal cord re-treatments using photon and proton based radiotherapy: LQ-derived tolerance doses. Phys Med 2019.
[44] Choi CY, Adler JR, Gibbs IC, et al. Stereotactic radiosurgery for treatment of spinal metastases recurring in close proximity to previously irradiated spinal cord. Int J Radiat Oncol Biol Phys 2010;78(2):499–506.
[45] Huo M, Sahgal A, Pryor D, et al. Stereotactic spine radiosurgery: Review of safety and efficacy with respect to dose and fractionation. Surg Neurol Int 2017;8:30.
[46] Foerster R, Cho BCJ, Fahim DK, et al. Histopathological findings after reirradiation compared to first irradiation of spinal bone metastases with stereotactic body radiotherapy: a cohort study. Neurosurgery 2018.