Chapter 16
Spinal Cord and Cauda Equina Compression

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Abstract Metastatic spinal cord compression (MSCC), diagnosed in 3–7 % of cancer patients, is a dreaded complication of metastatic cancer which must be diagnosed early and treated promptly to avoid progressive pain, paralysis, sensory loss and sphincter dysfunction in the patients. Magnetic resonance imaging is the best tool for diagnosing MSCC. Radiotherapy (RT) remains the treatment of choice in the majority of cases whereas surgery is advised only in selected patients. Hypofractionation schedules are safe and effective in MSCC. Although the most appropriate RT fractionation schedule remains unclear, many studies have shown that the choice of treatments should be matched to the prognosis of affected patient. When diagnosis of MSCC is made, steroids are generally prescribed to control edema and lessen pain. New techniques such as radiosurgery and stereotactic RT may be of benefit in high selected patients, including those with recurrent MSCC.

Keywords Bone metastases • Spinal cord compression • Cauda equina compression • Diagnosis • Surgery • Radiotherapy • Steroids • Stereotactic radiotherapy

16.1 Definition and Incidence

Metastatic spinal cord compression (MSCC) is one of the most dreaded complications of metastatic cancer. Its natural history, if untreated, is progressive pain, paralysis, sensory loss, and sphincter incontinence in patients. Although MSCC can be classified as intramedullary, leptomeningeal and extradural, in clinical practice extradural compression is the most frequent event. Moreover, several studies have shown that

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MSCC occurs at multiple non contiguous levels in 10–38 % of cases and the tumor is usually located in the anterior or antero-lateral spinal canal [1].

The definition of MSCC has changed over the last few decades and has both clinical and radiographic criteria and encompasses the anatomy of the cord as well the cauda equina. The Princess Margaret Hospital of Canada defines MSCC as: "compression of the dural sac (spinal cord and/or cauda equina) and its content by an extradural tumor mass. The minimum evidence for cord compression is indentation of the theca at the level of clinical features (i.e., local or radicular pain, weakness, sensory disturbance, and/or sphincter dysfunction)" [2]. Autopsy studies suggest that approximately one third of patients with solid tumors may have metastases to the spine, but the clinical evidence of MSCC is estimated in 3–7 % of patients. Approximately 50 % of MSCC cases in adults arise from breast, lung, or prostate cancer, but has also been described in patients with lymphoma, melanoma, renal cell carcinoma, thyroid carcinoma, sarcoma, and myeloma. In children the most common tumors are sarcoma, neuroblastoma and lymphoma. The most frequently involved site is the thoracic spine (59–78 %), followed by the lumbar spine (16–33 %) and the cervical spine (4–13 %) [3, 4].

16.2 Physiopathology

In the majority of cases, vertebral body metastases can produce spinal cord or cauda equina compression in two ways. The first results from continued growth and obliteration of the marrow space with expansion into the epidural space, producing impingement on the anterior thecal sac and its surrounding venous plexus. Alternatively, destruction of cortical bone by the tumor can result in vertebral body collapse with posterior displacement of bony fragments into the epidural space and epidural venous plexus. The pathophysiology of MSCC is vascular in nature because the compression of the epidural venous plexus leads to venous stasis, consequent hypoxia, and increased vascular permeability. This edema impairs spinal cord function which results in weakness and sensory impairment. In more advanced stages, the increased interstitial edema combined with progressive direct physical pressure on the spinal cord by the expanding mass, ultimately leads to ischemia of white matter and permanent neurologic loss [5].

16.3 Clinical Presentation

Spinal cord and cauda equina compression, once established, is usually highly symptomatic (Table 16.1). Pain is the most common symptom and accompanies in approximately 95 % of adults and 80 % of children with MSCC, and usually precedes the diagnosis by days to months [6]. Classic pain syndromes that affect patients were: local, mechanical, and radicular.

Table 16.1 Clinical symptoms and signs in spinal cord and cauda equina compression

Symptoms/signs	First symptom (%)	Symptom at diagnosis (%)	Sign at diagnosis (%)
Back pain	96	96	63
Weakness	6	76	87
Anomalies of reflexes	0	0	65
Autonomic dysfunction	0	57	57
Hypoesthesia	1	51	78
Ataxia	2	5	7

Local pain (i.e., back or neck pain) depends on expansion, destruction, or fracture of the involved vertebral elements and radicular pain is caused by compression of the nerve roots or cauda equina. Several characteristics distinguish it from the pain of degenerative joint disease. The first may arise at any level, whereas the second one rarely occurs outside the low cervical or low lumbar spine. It is usually described as a persistent "gnawing" emanating from the region or segment of the spine affected by metastatic disease. It is hypothesized that growth of the metastatic tumor, most commonly located in the posterior vertebral body, leads to periosteal stretching and/or a local inflammatory process that stimulates the pain fibers within the spinal periosteum Recumbence alleviates the pain of degenerative joint disease but frequently aggravates that of MSCC. Usually, this pain respond to steroids administration [7].

Mechanical pain, also known as axial back pain, is aggravated with movement, activity, or simply increasing weight-bearing forces on the spinal segment affected. Metastases that result in vertebral body damage (e.g., deformity, collapse) may result in spinal instability, which likely results in muscle, tendon, ligament and/or joint capsule strain and ensuing symptoms of mechanical pain. Unfortunately, such discomfort is usually refractory to narcotics and steroids [8].

Radicular pain may occur when vertebral metastases compress or irritate a nerve root, yielding pain in the dermatomal distribution of the involved root that is often described as "shooting," or "stabbing." Interestingly, dysesthetic/neuropathic pain may also arise when patients possess intradural extramedullary disease, creating pain that may be described as an "intense burning" sensation [7-9].

Neurological symptoms are common in patients with MSCC and weakness is the second most common symptom at presentation, usually follow the development of local or radicular pain and generally progress to plegia over a period of hours to days [3, 10]. Other symptoms of MSCC are sensory loss and incontinence, which typically develop after the pain.

Urinary retention, a common occurrence in patients who receive narcotics, is an atypical presentation without spinal pain or neurologic signs [1, 3]. Neurological status at the time of diagnosis, particularly motor function, has been shown to correlate with prognosis for these patients, thus reinforcing the concept that early diagnosis and prompt therapy are powerful predictors of outcome. Sensory disturbances such as anesthesia, hyperesthesia, and/or parasthesia typically occur in correlation with motor dysfunction. In this way, patients with radicular pain or weakness may also complain of sensory abnormalities in the same dermatomal distribution, while patients

with myelopathy may elicit a sensory level across the chest or abdomen. Particularly, patients with MSCC of the thoracic cord may present complaining only of discomfort around the chest, described as if they were being restricted by a "tight shirt" or "corset."

16.4 Diagnostic Work-up

Initial evaluation should begin with a detailed medical history, clinical examination, and directed laboratory tests. Assessment and documentation of bowel/bladder function, motor weakness, and sensory deficits are critical. The imaging armamentarium available includes plain radiography (RX), computed tomography (CT), magnetic resonance imaging (MRI), bone scan (BS), single-photon emission CT (SPECT), and positron emission tomography (PET). In the setting of complete subarachnoid block, myelography may increase the risk of neurologic deterioration.

Radiography can be a first tool as a screening test, by revealing lytic or sclerotic areas of bone, and vertebral deformity [11]. Bone destruction and substantial sclerosis are reliable indicators of metastases. However, vertebral body collapse can be associated with non-neoplastic lesions in up to 22 % of cases [17] and in approximately the half of examines these lesions can be missed on RX alone [11].

Computed tomography with 3-dimensional reconstruction provides excellent detail of the bony anatomy of the spine. Also, CT angiography can visualize the vertebral arteries in the foramen transversarium and as they enter the cranium, which assists surgical decision making and patient safety [12]. The angulation, rotation, and overall instability of a fracture, the extent of erosion of the vertebral body, pedicles, and posterior elements, and the degree of osteoblastic canal compromise are well visualized on CT.

Magnetic resonance imaging is considered the gold standard imaging modality for assessing spinal metastatic disease. It is more sensitive than standard radiographs, CT, and BS in detecting metastatic lesions in the spine [13]. Such sensitivity is due to the fact that MRI allows for superior resolution of soft-tissue structures such as intervertebral discs, the spinal cord and nerve roots, meninges, and paraspinal musculature. Moreover, considering that more than 85 % of patients have multiple-level involvement, MRI can show multiple levels of cord impingement in one examination. It is worthy to note that MRI diagnoses MSCC in 32–35 % of patients with back pain, bone metastases, and a normal neurologic examination [14]. In the pre-MRI era, myelography and CT were the imaging modalities of choice for the diagnosis of MSCC, and CT remains the best exam when MRI is not available. MRI has a sensitivity of 93 %, a specificity of 97 %, and an overall diagnostic accuracy of 95 % in detecting MSCC [4]. The advantages of MRI include its noninvasive ability to image soft tissue anatomy in detail, its ability to image multiple levels of cord impingement in one examination, and consequently, its usefulness in planning local treatment.

Nuclear imaging include BS, SPECT, and PET; BS is the oldest technique and almost 50 % of its results are false-negative for bone metastases, particularly in case

of vertebral medullary space involvement [15]. Moreover, BS does not accurately distinguish between pathologic and non-pathologic fractures. The PET is now more commonly used for whole body metastatic surveys and as a staging technique in patients with known systemic cancer. A recent comparison of BS, SPECT, and PET found that PET was as accurate as MRI [16]. However, poor spatial resolution necessitates concomitant use of CT and because of limited availability, resources, and study evidence SPECT and PET are not part of the standard evaluation.

16.5 Prognostic Factors and Survival

Prognosis is above all related to early diagnosis and therapy. Clinical risk factors for patients with suspected MSCC must be specific and sensitive for complete patient management. Back pain, an early and sensitive indicator of MSCC, is a non specific symptom, whereas signs consistent with actual spinal cord injury as weakness, paresis and plegia are more specific, but once they become evident the neurological outcome may be poor regardless of treatment. Many clinical variables are reported as prognostic factors for patients' post treatment ambulatory function and survival, but early diagnosis and prompt therapy are powerful predictors of outcome. In fact, MSCC patients able to walk and with a good sphincter function at the time of diagnosis have a higher probability of remaining ambulant and of a longer survival after treatment [3]. Favourable or radiosensitive cancers (i.e., breast and prostate carcinomas, myeloma and lymphoma) rather than unfavourable or less radiosensitive cancers (i.e., lung, bladder, and kidney carcinomas) are also significantly associated with a better outcome [17]. There could be various reasons to explain the better prognosis related to so called favourable histologies: (i) the better natural history, (ii) the higher response rate in presence of paraparesis or paraplegia and/or sphincter disturbance, (iii) a slower development of motor deficits before radiotherapy (RT), (iv) the longer interval between diagnosis of the primary malignancy and occurrence of MSCC. All these characteristics related to tumors with favourable histology were described as predictive of a better, functional outcome. Although Barcena's review reported location of tumour within the spinal canal, general medical status of the patients, and therapy used, as factors potentially determining functional prognosis in patients with MSCC, no other prospective published trials has shown the importance of these factors [18]. Some authors showed that patients with bone fracture greater than 50 % at the level of spinal cord compression had a poor response to RT compared to patients who had a less than 50 % compression fracture. However, considering that no studies reported the patient pretreatment motor status, no firm conclusions can be drawn [19, 20]. Nevertheless, the presence of vertebral body collapse is not an important prognostic variable if treatment selection is accurate (i.e., surgery before RT when there is bone impingement on the cord or nerve roots, and/or when stabilization is necessary) [19, 20] (Table 16.2).

The speed of neurologic deficit onset can condition functional outcome which is significantly better with slower development of motor dysfunction before RT.

Table 16.2 Prognostic factors of metastatic spinal cord compression

Major:
Early diagnosis and prompt therapy
Minor:
Post-treatment motor function
Tumor histology
Response to steroids
Performance status
Time from diagnosis of the primary tumor to appearance of spinal cord compression
Time from development of motor deficits to treatment

One study evidenced that ambulatory recovery occurred in 86 % and 35 % of patients with a history of >14 days compared with 1–7 days, respectively [20]. Early detection and treatment when the patient is still able to walk result in the highest chance of ambulation. In MSCC the aim of treatment is to improve the patients' quality of life through control of back pain and preservation or recovery of motor and sphincter functions. Although it could be questioned whether local treatment increases patients' survival, there is a tight relationship between survival time and functional status. In fact, MSCC patients who have no motor dysfunction live longer than paraparetic and paraplegic ones, and generally die of systemic tumors rather than local progression at the spine.

Survival after MSCC is principally related to primary tumor type ranging from 17 to 20 months for breast, prostate and myeloma to only 4 months for lung cancer [21]. If untreated, the majority of patients with MSCC become paraplegic with a median survival time of 2–3 months [22].

16.6 Treatment

As already highlighted, treatment success is related to the severity of the epidural disease and to the patient's clinical condition at the time of diagnosis, it is important to confirm diagnosis early and to begin treatment before significant myelopathy develops. Treatment of MSCC can be surgery followed by RT or RT alone. The choice of treatment depends on patient selection according to specific factors reported in Fig. 16.1 and discussed below. When a diagnosis of MSCC is made, the first intervention is generally steroids to control edema and lessen pain.

16.7 Surgery

Surgery plays an important role in selected cases. Patchell et al. published the results of a trial that randomized patients to surgery and post operative RT or RT alone [23]. The study aimed to recruit 200 patients was prematurely closed because an interim

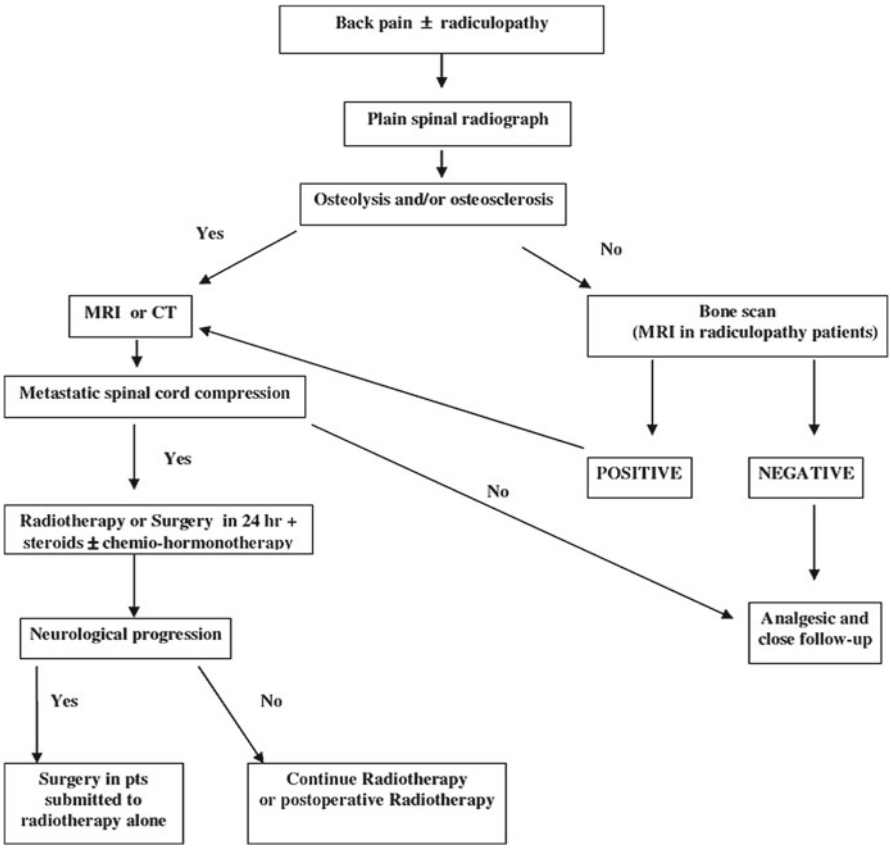

Fig 16.1 Flow chart of early diagnosis and therapy in patients with metastatic spinal cord compression (Legend, *MRI* magnetic resonance imaging, *CT* computed tomography)

analysis showed a significant improvement in ambulatory rate in the combined surgery and RT arm. The published results are therefore based on 101 patients accrued from seven centres over a 10-year period with 70 of the patients recruited from one centre. The study has been criticized because of the poor results in the RT-alone arm which contrast with published RT data and, furthermore, since mechanical causes of cord compression were not stipulated as an exclusion criteria, some patients may have been treated inappropriately with RT alone [2, 24]. A secondary data analysis of this study published in 2009 looked at age stratification and demonstrated a tight interaction between age and treatment effect, such that as age increases, the benefit of surgery is diminished. Statistical analysis showed that there was no difference in outcome between treatments for patients aged 65 years or more [25]. A meta-analysis of surgery versus conventional RT for MSCC published in 2005 identified 4 RT and 24 surgical trials involving 578 and 1,020 patients, respectively. Resected patients obtained a better recover ambulation (85 % vs. 64 %) and pain control (90 % vs. 70 %)

respect to RT alone. No prognostic and predictive factors were adjusted in this analysis [26]. However, the surgical data used in this meta-analysis contain primarily uncontrolled cohort studies and preceded the Patchell et al. publication. Conversely, an analysis performed retrospectively on 122 patients treated with surgery followed by RT matched 11 known prognostic factors to 244 patients submitted to RT alone found that treatment approach had no impact in any of the outcomes examined (i.e., improvement in motor function, post-treatment ambulatory rates, recovery of ambulation among nonambulatory patients, 1-year local control and 1-year overall survival [27].

Recently a systematic review, which analyzed data published from 2004 to 2011, concluded that surgery can be considered for patients with a good prognosis who are medically operable, and technical factors that allow proper fixation/stabilization need to be considered for any surgical technique adopted [28].

Finally, on the basis of the literature evidence, it can be concluded that initial surgical resection followed by RT should be considered for a carefully selected group of patients that are affected by single-level MSCC and neurological deficits and controlled or absent primary and metastatic disease elsewhere. Other possible indications for surgery include stabilization, vertebral body collapse causing bone impingement on the cord or nerve root, compression recurring after RT, and an unknown primary requiring histological confirmation for diagnosis. Nevertheless, when there are diagnostic doubts, CT-guided percutaneous vertebral biopsy can be an alternative to open surgery to avoid surgical side effects, and reduce incisional pain and postoperative recovery period.

Regarding surgical approach, laminectomy should be abandoned and every effort should be made to minimize the surgical toxicity assuring an adequate decompression and a spinal stability. In fact, laminectomy does not remove the tumoral mass and, when there is vertebral body collapse, it may also cause post surgery spinal instability. Generally, RT must be administered 7–10 days after surgery, either after no grossly complete resection or as an adjuvant treatment after a macroscopic radical ablative surgical procedure [1, 28].

16.8 Radiotherapy

Although RT is an effective approach for the majority of MSCC patients, the optimal radiation schedule remains unknown. Except for particular circumstances, the use of conventional fractionated RT (2 Gy per day to a total dose of 30–50 Gy in 3–5 weeks) has been abandoned in favour of RT regimens requiring a smaller number of fractions. Since 2005, two phase III randomized multicentre Italian trials have been published [29, 30]. The first trial compared a short-course regimen (i.e., 8 Gy repeated after 1 week to a total dose of 16 Gy) to a split-course regimen (i.e., 5 Gy × 3, 4 days rest and then 3 Gy × 5) [29]. The second one compared the same short-course regimen to 8 Gy in a single fraction [30]. It is worthy to note that both of these trials were performed on patients with short life expectancy (≤6 months),

and that responders maintained function until death. While both hypofractionated RT regimens adopted resulted effective, the authors concluded that 8-Gy single fraction can be the best option considering that it is well tolerated, effective and convenient in this setting of patients. Published retrospective and prospective non randomized studies support the above randomized data in that no dose-fractionation schedule has demonstrated a higher ambulation rate. However, considering that in some case the long-course RT regimens were associated to an increase of local control duration in MSCC patients, some authors argument in favour of more prolonged RT regimens for patient selected on the basis of a better prognosis [31-33].

Recently, it was published a score predicting post-RT ambulatory status [34]. It was developed based on 2,096 retrospectively evaluated MSCC patients. Tumor type, interval between tumor diagnosis and MSCC, presence of other bone or visceral metastases at the time of RT, pre-treatment ambulatory status, and duration of motor deficits were the six prognostic factors resulting significant for survival and ambulatory function.

Finally, evidence suggests that until further randomised data are available, short-course/single fraction regimens (e.g., 5×4 Gy, 2×8 Gy, or 1×8 Gy) can be used for patients with short life expectancy, while fractionated, higher dose schedules (e.g., 10×3 Gy or greater) should be considered for patients with better prognosis.

Radiotherapy planning is optimal when an MRI is available. With MRI, vertebral and paravertebral involvement can be better defined with respect to all other radiological procedures. Radiation portals should be centered on the site of epidural compression and accurate 3D-conformal RT should be used in the majority of cases. In the 16–25 % of cases who develop recurrent MSCC after RT, 64 % of early recurrences are within two vertebral bodies of the site of initial compression [1]. Therefore, radiation portals should be extended two vertebral bodies above and two vertebral bodies below the site of compression. Adjacent sites of bony involvement and paravertebral masses should also be encompassed in the treatment volume.

16.9 Steroids

Generally, in MSCC patients RT is administered with concomitant steroids to lessen back pain, prevent progressive neurologic symptoms, and reduce RT-induced spinal edema [1]. Steroids should be given immediately when the clinical and radiological diagnosis of MSCC is obtained. Dexamethasone is the most frequently used drug, although the use of methylprednisolone is also reported [35]. The dexamethasone dose ranges from moderate (16 mg/day in 2–4-times daily parenteral or oral divided doses) to high (36–96 mg/day), sometimes preceded by an intravenous bolus of 10–100 mg [1, 35]. Steroids are usually tapered over 2 weeks. No study has been published comparing high- to moderate- dose of dexamethasone. There is only one randomized clinical trial comparing high dose dexamethasone to no drug in 57 patients with MSCC treated with RT [36]. This trial evidenced that high dose dexamethasone significantly improves post treatment ambulation, but associated to

a certain probability (11 %) of high toxicity. A phase II trial showed the feasibility of treating patients with MSCC, no neurologic deficits, or only radiculopathy, and no massive invasion of the spine at MRI or CT with RT (10×3 Gy) without steroids [37]. However, in clinical practice, considering that published studies have shown no difference in outcome between high- and moderate- dose dexamethasone, and the relatively high incidence of side effects from steroids, above all in patients with diabetes mellitus, hypertension, and peptic ulcer a moderate dexamethasone dose of 16–32 mg/day is suggested for symptomatic MSCC patients [38].

16.10 Chemotherapy and Hormone Therapy

For treatment of MSCC, chemotherapy or hormone therapy can be used in combination with RT, or alone in adults who are not surgical or radiation candidates but who have sensitive tumors such as lymphoma, small cell lung carcinoma, myeloma, breast, prostate, or germ cell tumors. In children chemotherapy is the primary treatment for chemo-responsive tumors [1].

16.11 Promise of Newer Technologies

The majority of MSCC patients have low performance status, paraparesis, paraplegia and/or other prognostic factors associated with a short life expectancy. In these cases palliative short course or single fraction RT regimens represent the standard treatment. A more aggressive RT may eventually be justifiable for patients selected according to good performance status, oligometastatic disease and longer life expectancy. In this subset of patients a higher RT dose can be prescribed using special techniques. Linear accelerator technology has evolved with multileaf collimation, intensity modulated irradiation, systems of image guidance, and robotic technology. Radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) have emerged as new treatment options in the multidisciplinary management of metastases located within or adjacent to the vertebrae and spinal cord. They provide attractive options to deliver high dose per fraction radiation, typically in single dose (e.g., 10–16 Gy) or in hypofractionation (e.g., 9 Gy×3 fractions or 6 Gy×5 fraction) [39].

In contrast to other RT techniques, SRS and SBRT allow treatment to the involved vertebrae and spinal cord with a high radiation dose, reducing irradiated volume, and sparing uninvolved segments [39, 40]. The role of SRS and SBRT for epidural decompression in selected groups of MSCC patients is under evaluation together with the potential higher risk of RT-induced myelopathy. These techniques cannot be used as an emergency procedure given the time taken for planning and treatment verification. The need for sophisticated and expensive radiation units, which are offered only in few specialized centres, limits the routine use of SRS and SBRT [41-43].

16.12 Conclusion

Early diagnosis and prompt therapy are powerful predictors of outcome in MSCC. The best diagnostic tool for diagnosis and treatment planning is MRI. Generally, RT is accepted as the first line treatment for the majority of patients with spinal cord and cauda equina compression, and surgery should be considered for a carefully selected group of patients. As suggested by many prospective clinical trials, hypofractionated RT regimen can be considered the regime of choice, while more protracted RT schedules can be used in selected MSCC patients with a predicted long life expectancy. The new technologies of irradiation provide an interesting opportunity for selected patients, though it is much more expensive, and can be administered only in highly specialized radiation centers.

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