Mini-Review | Palliative Medicine and Palliative Care for Incurable Cancer

Reirradiation of metastases of the central nervous system: part 2—metastatic epidural spinal cord compression

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Abstract: An increasing number of patients irradiated for metastatic epidural spinal cord compression (MESCC) experience an in-field recurrence and require a second course of radiotherapy. Reirradiation can be performed with conventional radiotherapy or highly-conformal techniques such as intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), and stereotactic body radiation therapy (SBRT). When using conventional radiotherapy, a cumulative biologically effective dose (BED) ≤120 calculated with an α/β value of 2 Gy (Gy_2) was not associated with radiation myelopathy in a retrospective study of 124 patients and is considered safe. In that study, conventional reirradiation led to improvements of motor deficits in 36% of patients and stopped further symptomatic progression in another 50% (overall response 86%). In four other studies, overall response rates were 82–89%. In addition to the cumulative BED or equivalent dose in 2 Gy fractions (EQD2), the interval between both radiotherapy courses <6 months and a BED per course ≥102 Gy_2 (corresponding to an EQD2 ≥51 Gy_2) were identified as risk factors for radiation myelopathy. Without these risk factors, a BED >120 Gy_2 may be possible. Scoring tools have been developed that can assist physicians in estimating the risk of radiation myelopathy and selecting the appropriate dose-fractionation regimen of re-treatment. Reirradiation of MESCC may also be performed with highly-conformal radiotherapy. With IMRT or VMAT, rates of pain relief and improvement of neurologic symptoms of 60–93.5% and 42–73%, respectively, were achieved. One-year local control rates ranged between 55% and 88%. Rates of myelopathy or radiculopathy and vertebral compression fractures were 0% and 0–9.3%, respectively. With SBRT, rates of pain relief were 65–86%. Two studies reported improvements in neurologic symptoms of 0% and 82%, respectively. One-year local control rates were 74–83%. Rates of myelopathy or radiculopathy and vertebral compression fractures were 0–4.5% and 4.5–13.8%, respectively. For SBRT, a cumulative maximum EQD2 to thecal sac ≤70 Gy_2, a maximum EQD2 of SBRT ≤25 Gy_2, a ratio ≤0.5 of thecal sac maximum EQD2 of SBRT to maximum cumulative EQD2, and an interval between both courses ≥5 months were associated with a lower risk of myelopathy. Additional prospective trials are required to better define the options of reirradiation of MESCC.

Keywords: Metastatic epidural spinal cord compression (MESCC); reirradiation; conventional radiotherapy; highly-conformal radiotherapy

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Introduction

A considerable number of cancer patients develop spinal metastases with epidural spinal cord compression (MESCC). "True" MESCC can be considered compression or infiltration of the spinal cord associated with neurologic deficits (1). Many patients with MESCC receive radiotherapy alone or following decompressive surgery. Since the introduction of novel targeted therapies and immunotherapies for cancer treatment have led to longer survival, an increasing number of patients experience a recurrence in the previously irradiated segment of the spinal cord (in-field recurrence) and require a second course of radiotherapy. Spinal reirradiation can be challenging, since the cumulative dose of both radiotherapy courses may exceed the tolerance dose of the spinal cord. Thus, reirradiation carries a higher risk of radiation myelopathy, which may be associated with severe pain and neurologic deficits. This narrative review summarizes the outcomes after a second course of radiotherapy (first reirradiation) for MESCC, including response to radiotherapy, local control, tolerance doses, and toxicity, and aims to identify patients, in whom reirradiation appears comparably safe.

Methods

To contribute to these aspects, a comprehensive search on PubMed was performed from 1990 to 2023 using the terms "metastatic spinal cord compression and re-irradiation", "metastatic epidural spinal cord compression and re-irradiation", "spinal cord compression and re-irradiation", "metastatic spinal cord compression and reirradiation", "metastatic epidural spinal cord compression and reirradiation", and "spinal cord compression and reirradiation". Papers with an English abstract considered relevant were included, regardless of the language.

Tolerance doses of the spinal cord to radiotherapy

According to the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC), maximum doses to the spinal cord of 50, 60, and 69 Gy (conventionally fractionated radiotherapy) are associated with a risk of myelopathy of 0.2%, 6%, and 50%, respectively (2). Kirkpatrick *et al.* reported a risk of myelopathy, defined as grade ≥2 myelitis (Common Terminology Criteria for Adverse Events v3.0), of <1% at 54 Gy and <10% at 61 Gy, respectively to the full-thickness cord, when using conventional fractionation (1.8–2.0 Gy per fraction) (3). However, these authors used an unusual α/β value of 0.87 Gy instead of 2.0 Gy. Moreover, after stereotactic body radiation therapy (SBRT) with 1× 13 or 20 Gy in 3 fractions (maximum doses), the risk of myelopathy appeared <1%. Sahgal *et al.*, who evaluated the spinal cord tolerance to SBRT using one to five fractions, found that each of the dose-fractionation regimens 1× 12.4–14.0 Gy, 2× 8.5 Gy, 3× 6.77 Gy, 4× 5.75 Gy, and 5× 5.06 Gy, was estimated to have a myelopathy risk of 1–5% (4).

Reirradiation of MESCC using conventional radiotherapy

In 1990, Magrini *et al.* compared five patients with Hodgkin's disease irradiated twice at the spinal cord (cumulative doses of 50–70 Gy with doses per fraction of 1.8 or 2.0 Gy) to seven patients with comparable baseline characteristics (5). Patients were followed for more than 10 years and had no or minor neurologic symptoms. No differences were found on magnetic resonance imaging, but on electrophysiological studies a clear difference between cases and controls was identified. Schiff *et al.* investigated 54 patients who underwent at least two courses of radiotherapy to the same spinal segment and had epidural involvement at the time of reirradiation (6). Cumulative doses of both courses ranged between 36.5 and 80.89 Gy (median, 54.25 Gy), and doses per fraction between 1.8 and 3.0 Gy (median, 2.33 Gy). Forty (74%) and 42 patients (78%), respectively, were ambulatory at the start and at the end of reirradiation. Thirty-seven patients (69%) were still ambulatory after a median of 4.7 months. It was concluded that reirradiation frequently preserved ambulatory status and was associated with a very low risk of myelopathy.

In 2002, Grosu *et al.* reported the data of eight patients with bone metastases who received a second course of palliative radiotherapy to the spinal cord (7). Doses of the first course ranged between 29 and 50 Gy (median, 38 Gy) with doses per fraction of 1.25–3.0 Gy. Doses of the second course were 29–38 Gy (median, 30 Gy) with doses per fraction of 1.8–4.0 Gy. Median cumulative dose of both courses was 67.5 (range, 59–88) Gy. The median interval between both courses was 30 (range, 6–63) months. Of seven patients with pain, 6 patients (86%) experienced at least partial relief, and 4 patients (57%) achieved complete relief. Both patients with motor

Table 1 Tools to estimate the risk of radiation myelopathy following reirradiation with conventional radiotherapy

Nieder *et al.* (8) who used the BED			Doi *et al.* (9) who used the EQD2		
Risk factor	Characteristics	Scoring points	Risk factor	Characteristics	Scoring points
Interval between 1st and 2nd RT course	≥6 months	0	Interval between 1st and 2nd RT course	≥6 months	0
	<6 months	4.5		<6 months	4.5
BED of 1st or 2nd RT course	<102 Gy_2	0	EQD2 of 1st or 2nd RT course	<51 Gy_2	0
	≥102 Gy_2	4.5		≥51 Gy_2	4.5
Cumulative BED, both courses of RT	≤120 Gy_2	0	Cumulative EQD2, both courses of RT	≤60 Gy_2	0
	120.1–130 Gy_2	1		60.1–65 Gy_2	1
	130.1–140 Gy_2	2		65.1–70 Gy_2	2
	140.1–150 Gy_2	3		70.1–75 Gy_2	3
	150.1–160 Gy_2	4		75.1–80 Gy_2	4
	160.1–170 Gy_2	5		80.1–85 Gy_2	5
	170.1–180 Gy_2	6		85.1–90 Gy_2	6
	180.1–190 Gy_2	7		90.1–95 Gy_2	7
	190.1–200 Gy_2	8		95.1–100 Gy_2	8
	>200 Gy_2	9		100.1–105 Gy_2	9
				105.1–110 Gy_2	10

Tools according to Nieder *et al.* (8) who used the BED (permission obtained from Elsevier through Copyright Clearance Center's RightsLink® service), and according to Doi *et al.* (9) who used the EQD2 (open access article licensed under a Creative Commons Attribution 4.0 International License; http://creativecommons.org/licenses/by/4.0/). Risk groups: 0–3 points = low risk; 4–6 points = intermediate risk; >6 points = high risk of radiation myelopathy. BED, biologically effective dose; EQD2, equivalent dose in 2 Gy fractions; RT, radiotherapy; Gy_2, doses calculated with an α/β value of 2 Gy.

deficits prior to reirradiation improved and had normal strength following re-treatment. Radiation myelopathy was not observed during follow-up [median, 16 (range, 5–44) months] after reirradiation. Nieder *et al.* presented a review of 40 patients from eight previous reports reirradiated at the spinal cord for different scenarios (8). Biologically effective doses (BEDs) were re-calculated with an α/β value of 2 Gy (Gy_2) for cervical and thoracic spinal cord and 4 Gy (Gy_4) for lumbar spinal cord, respectively. A dose of 50 Gy in 2.0 Gy per fraction represented a BED of 100 Gy_2 or 75 Gy_4. Median cumulative BED was 135 (range, 108–205) Gy_2, and the median interval between both courses was 20 months. Radiation myelopathy occurred in 11 patients (27.5%) after a median of 11 (range, 4–25) months. Nine of these patients had received a BED of ≥102 Gy_2 in one course, and two patients were reirradiated already after 2 months. In patients with a BED <102 Gy_2 per course and an interval between both courses >2 months, myelopathy did not occur after a cumulative BED of ≤135.5 Gy_2 (n=19) or 136–150 Gy_2 (n=7). Based on cumulative BED, BED per radiation course (<102 *vs.* ≥102 Gy_2), and the interval between both courses (<6 *vs.* ≥6 months), a risk score was developed (*Table 1*). Three groups (≤3, 4–6, and >6 points) were identified with a myelopathy risk of 0% (0 of 24 patients), 33% (2/6 patients), and 90% (9/10 patients), respectively. In 2006, Nieder *et al.* presented an update of their previous study with data from an additional 38 patients (10). Myelopathy rates for low-risk, intermediate-risk and high-risk patients were 3% (1/30 patients), 25% (2/8 patients), and 90% (9/10 patients), respectively.

In 2005, a retrospective study was presented by our group including 62 patients reirradiated for an in-field recurrence of MESCC with motor deficits (11). Reirradiation was performed after median 6 (range, 2–42) months with 1× 8 Gy in 34 patients (following 1× 8 Gy or 5× 4 Gy), 5× 3 Gy in 15 patients (following 1× 8 Gy or 5× 4 Gy), or

5× 4 Gy in 13 patients (following 1× 8 Gy), respectively. The cumulative BED ranged between 80 and 100 Gy_2. Overall response (defined as improvement or at least no further progression of motor deficits) to reirradiation was 85% (53 of 62 patients alive) at 1 month, 90% (51 of 57 patients) at 3 months, and 97% (37 of 38 patients) at 6 months following reirradiation. Improvement rates were 40%, 44%, and 55%, respectively. Moreover, 6 of 16 non-ambulatory patients (38%) regained the ability to walk. A second in-field recurrence of MESCC and radiation myelopathy were not observed during a median follow-up of 8 (range, 2–42) months. Reirradiation was considered effective and, if the cumulative BED was ≤100 Gy_2, also safe. Another retrospective study included 12 additional patients, of whom 10 patients received reirradiation with a longer-course program, namely 10× 2 Gy (n=4), 12× 2 Gy (n=3), or 17× 1.8 Gy (n=3) (12). The cumulative equivalent doses in 2 Gy fractions (EQD2s) were ≤50 Gy_2 in 62 patients, 56–60 Gy_2 in six patients, and >60 Gy_2 in six patients. Overall response and improvement rates regarding motor function were 85% and 39%, respectively. On multivariable analysis, better functional outcome was significantly associated with favorable primary tumor type (P=0.013) and slower development of motor deficits prior to reirradiation (P=0.037). Six of 16 non-ambulatory patients (37%) became ambulatory following reirradiation. Radiation myelopathy was not observed during the median follow-up period of 9 (range, 2–52) months. Thus, reirradiation was effective and appeared safe after a cumulative EQD2 of ≤50 Gy_2. In 2008, we presented a retrospective series of 124 patients reirradiated for motor deficits due to an in-field recurrence of MESCC, including 50 new patients (13). Dose-fractionation regimens of reirradiation included 1× 8 Gy (n=48), 5× 3 Gy (n=29), 5× 4 Gy (n=30), 7× 3 Gy (n=3), 10–12× 2 Gy (n=11), and 17× 1.8 Gy (n=3). The cumulative BED of both radiotherapy courses ranged between 77.5 and 142.6 Gy_2 and ≤120 Gy_2 in 114 patients (92%). Rates of overall response and improvement of motor function were 86% and 36%, respectively. In the multivariable analysis, functional outcome was significantly associated with a better effect of the first radiotherapy course (P=0.048), better performance status (P=0.020), slower development of motor deficits prior to reirradiation (P=0.002), and absence of visceral metastases (P<0.001). During the follow-up period of median 11 (range, 3–54) months in survivors, radiation myelopathy was not detected. A cumulative BED ≤120 Gy_2 was considered safe.

Since due to demographic change the proportion of elderly cancer patients aged ≥65 years is growing, we performed a separate retrospective study particularly focusing on this age group (14). Sixty patients were reirradiated for an in-field recurrence of MESCC associated with motor deficits. The interval between the radiotherapy courses was 6 (range, 2–45) months. Dose-fractionation regimens of reirradiation included 1× 8 Gy, 5× 4 Gy, 5–7× 3 Gy, and 10–12× 2 Gy. The cumulative BED ranged from 80 to 142.6 Gy_2, with 52 patients (87%) receiving ≤120 Gy_2. Following reirradiation, rates of at least no further progression and improvement of motor deficits were 89% and 42%, respectively. Radiation myelopathy and a second in-field recurrence of MESCC did not occur. Hence, elderly patients do benefit from reirradiation of MESCC similarly to younger patients.

More recently, the results of a phase 2 clinical trial of reirradiation with 6× 3 Gy to 10× 3 Gy were published (15). Of 22 patients with MESCC being enrolled, 11 were eligible for the primary endpoint (change in mobility between weeks 1 and 5 following reirradiation). The median time the patients were in the study was 2 (range, <1–40) months. Initially, the maximum cumulative BED was 100 Gy_2 if the interval between both radiotherapy courses was ≤6 months and was 130 Gy_2 (later reduced to 120 Gy_2) if the interval was >6 months. Overall response regarding mobility at 5 weeks was 81.8% (9 of 11 patients). One of 8 patients (12.5%) evaluable for late toxicities developed radiation myelopathy after cumulative 120 Gy_2. Another study included 32 patients free from radiation myelopathy after median of 12 months following reirradiation of the cervical or thoracic spinal cord (9). The median interval between both radiotherapy courses was 15 (range, 6–97) months. The maximum cumulative EQD2 ranged between 61.12 and 114.79 Gy_2 (median, 80.7 Gy_2). The cumulative EQD2 to 0.1 cc (spinal cord) ranged between 61.12 and 95.62 Gy_2 (median, 76.1 Gy_2). Nine patients received one course with a maximum EQD2 of ≥51 Gy, and five patients received one course with ≥51 Gy to 0.1 cc. Even at higher cumulative doses than those considered safe in previous studies, these patients did not develop radiation myelopathy. However, one should be aware that patients remaining alive are still at risk of experiencing this complication (9). Therefore, higher cumulative doses may not be recommended at this stage. The risk score developed by Nieder *et al.* using the cumulative BED and an updated version using the cumulative EQD2 can help physicians to choose the appropriate dose-fractionation regimen for reirradiation of

MESCC (8,9). In addition, Price *et al.* investigated repair of sublethal damage as function of time between the first radiotherapy course and reirradiation (16). Estimated sublethal damage repair was 0% for an interval <6 months and 50% for >1 year. Moreover, the authors found that the repair typically does not exceed 50%, regardless of the length of the interval between both courses ("conservative practices").

Reirradiation of MESCC using highly-conformal radiotherapy

During the last two decades, highly-conformal radiotherapy techniques including intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), SBRT, and proton therapy have been increasingly used for re-treatment of MESCC. In 2003, Milker-Zabel *et al.* presented the data of 18 patients (19 lesions) reirradiated with median 39.6 (range, 24–45) Gy of fractionated conformal radiotherapy or IMRT (median dose per fraction of 2.0 Gy) following primary treatment with conventional radiotherapy [median dose, 38 (range, 28–46) Gy] (17). Thirteen of 16 patients with pain (81%) experienced significant relief, and 5 of 12 patients with neurologic deficits (42%) showed improvement. After a median follow-up of 12.3 months, overall local control was 94.7%. Neurologic toxicity or vertebral compression fractures were not observed. The study by Damast *et al.* included 97 patients reirradiated for recurrent paraspinal metastases with image-guided IMRT (IG-IMRT) (18). Median dose of the primary radiotherapy was 30 Gy. Dose-fractionation regimens of IG-IMRT were 5× 4 Gy (n=42) or 5× 6 Gy (n=55). Forty-seven patients (48%) received upfront decompressive surgery. Forty-one patients were reirradiated for pain and/or neurologic symptoms. Sixteen of 35 evaluable patients (46%) reported significant pain improvement, and 11 patients (31%) achieved mild pain relief. One-year local failure rates were 45% after 5× 4 Gy and 26% after 5× 6 Gy. Radiation myelopathy was not observed; vertebral compression fractures occurred in 9 patients (9.3%). In the study of Navarria *et al.*, 31 patients were reirradiated (after a median of 10× 3 Gy) using VMAT to a median of 30 Gy in 12 fractions; six patients received upfront surgery (19). Twenty-nine patients (93%) experienced pain relief, and 13 of 15 patients (73%) with neurologic deficits improved. Acute and late toxicities were not observed. No second in-field recurrence occurred after a median follow-up of 9 (range, 6–24) months. Kawashiro *et al.* reported data of 23 patients reirradiated (mainly following 10× 3 Gy or 20× 2 Gy) with IMRT (median 24.5 Gy in 5 fractions) (20). Fifteen of 19 patients (79%) had pain relief, and 2 of 3 patients with motor deficits improved. Late complications were not found after a median follow-up of 10 (range, 1–54) months. In the study by Sasamura *et al.*, 40 patients (42 lesions) received reirradiation to 5× 5 Gy of IMRT following a median of 30 Gy in 10 fractions (21). Twenty-four patients (60%) reported pain relief, and 8 of 15 patients (53%) had neurological improvement. One patient (2.5%) developed a vertebral compression fracture. Myelopathy was not observed during the follow-up of median 9.7 (range, 1.1–42.8) months. Results of studies using IMRT or VMAT are summarized in *Table 2*.

Several studies used SBRT for reirradiation following conventional radiotherapy. In 2011, Mahadevan *et al.* reported the results of 60 patients (81 lesions) reirradiated with fractionated SBRT (3× 8 Gy or 5–6× 5 Gy) (22). Pain relief was achieved in 22 of 34 patients (65%). The four patients with motor deficits remained neurologically stable but did not improve. Radiation-related myelopathy and radiculopathy were not observed during a median follow-up of 12 (range, 4–36) months. Chang *et al.* used different regimens of SBRT in 54 reirradiated patients and indicated the margin dose (single equivalent) as 20.6±5.9 Gy (23). Rates of pain relief and 1-year local control were 86% and 81%, respectively. Myelopathy and radiculopathy did not occur, and the rate of vertebral compression fractures was <10% (mean follow-up, 17.3 months). Hashmi *et al.* used single-fraction SBRT to a median of 16.6 Gy (60% of patients) or fractionated SBRT to a median of 24 Gy in 3 fractions (40% of patients) for reirradiation following conventional radiotherapy to 10× 3 Gy in 215 patients (247 lesions) (24). Pain relief and 1-year local control rates were 74% and 83%, respectively. Myelopathy and vertebral compression fracture rates were 0% and 4.5%, respectively. In the study by Boyce-Fappiano *et al.*, 162 patients (237 lesions) received single-fraction SBRT to a median dose of 16 Gy following conventional radiotherapy to a median of 10× 3 Gy (25). Overall rates of pain relief and neurological response were 81% (67 of 83 patients) and 82% (9 of 11 patients), respectively. Myelopathy/radiculopathy and vertebral compression fractures occurred in 4.3% and 9.3% of patients, respectively. Ito *et al.* used SBRT to 24 Gy in 2 fractions for reirradiation following conventional radiotherapy with dose-fractionation regimens ranging between 1× 8 Gy and ≥50 Gy in 25 fractions (26). Median

Table 2 Results of studies that used IMRT or VMAT for reirradiation and reported symptom control rates

Reference [year]	No. of patients [lesions]	Regimens of ReRT	Rate of pain relief	Rate of improved neurologic deficits	1-year local control rate	Myelopathy/ radiculopathy	Rate of vertebral compression fractures
Milker-Zabel (17) [2003]	18 [19]	Median 39.6 (range, 24–45) Gy; median dose: 2.0 Gy/1 F	81%	42% (5/12 patients)	NA	0%	0%
Damast (18) [2011]	97	20 Gy/5 F or 30 Gy/5 F	77%	NA	55% (20 Gy); 74% (30 Gy)	0%	9.3% (9/97 patients)
Navarria (19) [2012]	31	Median 30 Gy/12 F	93.5%	73% (13/15 patients)	NA	0%	0%
Kawashiro (20) [2016]	23	Median 24.5 Gy/5 F	79%	67% (2/3 patients)	88%	0%	0%
Sasamura (21) [2020]	40 [42]	25 Gy/5 F	60%	53% (8/15 patients)	67%	0%	2.5% (1/40 patients)

IMRT, intensity-modulated radiation therapy; VMAT, volumetric modulated arc therapy; ReRT, reirradiation; NA, not available.

Table 3 Results of studies that used SBRT for reirradiation and reported symptom control rates

Reference [year]	No. of patients [lesions]	ReRT dose/ fractionation	Rate of pain relief	Rate of improved neurologic deficits	1-year local control rate	Myelopathy/ radiculopathy	Rate of vertebral compression fractures
Mahadevan (22) [2011]	60 [81]	24 Gy/3 F; 25–30 Gy/5 F	65%	0% (0/4 patients)	NA	0%	NA
Chang (23) [2012]	54	20.6±5.9 Gy	86%	NA	81%	0%	<10%
Hashmi (24) [2016]	215 [247]	Median 16.6 Gy/1 F; 24 Gy/3 F	74%	NA	83%	0%	4.5% (11/247 lesions)
Boyce-Fappiano (25) [2017]	162 [237]	Median 16 Gy/1 F	81%	81% (9/11 patients)	NA	4.3%†	9.3% (22/237 lesions)
Ito (26) [2021]	123 [133]	24 Gy/2 F	75%	NA	74%	4.5%‡	13.8% (17/123 patients)

†, including sensory changes/weakness/radiculopathy (3.1%), radiation myelopathy (0.6%), myelomalacia (0.6%), graded not reported (25); ‡, including radiation myelopathy (3.0%) and radiculopathy (1.5%), grade not reported (26). SBRT, stereotactic body radiation therapy; ReRT, reirradiation; NA, not available.

follow-up was 12 (range, 1–57) months. Rates of pain relief at 3, 6, and 12 months were 75%, 64%, and 59%, respectively. One-year local failure was 25.8%. Radiation-related neurotoxicity was found in 4.5% of patients, including myelopathy (3%) and radiculopathy (1.5%), and 13.8% experienced vertebral compression fractures. In addition, Ito *et al.* presented 17 patients (19 lesions) who received reirradiation with SBRT (25–30 Gy in 5 fractions) following SBRT to 24 Gy in 2 fractions (27). One-year local control was 100%, although 14 patients had radioresistant primary tumors. Late toxicity rates were comparably high, including 21% of radiculopathy and 11% of vertebral compression fractures. Results of studies using SBRT are shown in *Table 3*. When using SBRT for reirradiation of MESCC, unique risk factors for radiation myelopathy must be considered. Sahgal *et al.* found for reirradiation using SBRT with 1–5 fractions that a cumulative maximum EQD2 (α/β of 2 Gy) to the thecal sac ≤70 Gy_2, a maximum EQD2 of SBRT ≤25 Gy_2, a ratio of thecal sac maximum EQD2 of SBRT to the maximum cumulative EQD2 of ≤0.5, and a minimum interval until reirradiation of ≥5 months were associated with a lower risk of radiation myelopathy (4,28).

Limitations

When interpreting the current narrative mini-review, the corresponding limitations should be kept in mind, including the risk of selection biases related to authors' preferences and perspectives with respect to selection and interpretation of the studies available in the literature (29). A considerable number of the studies have a retrospective design and, therefore, an additional risk of selection biases. Another limitation is the wide range of follow-up periods, particularly in the studies investigating re-irradiation with highly-conformal techniques. Moreover, in case of SBRT with doses per fraction >10 Gy, the accuracy of the linear-quadratic model appears limited (5,30). Since alternative models suggested so far have not been validated in clinical settings, the linear-quadratic model is still the preferred model also for higher doses per fraction (5).

Conclusions

An increasing number of patients with MESCC experience in-field recurrences and require reirradiation. When using conventional radiotherapy, a cumulative BED ≤120 Gy_2 can generally be considered safe. In patients without risk factors like an interval between radiotherapy courses <6 months and/or BED per course ≥102 Gy_2/EQD2 per course ≥51 Gy_2, higher cumulative doses may be possible. Scoring tools to estimate the risk of radiation myelopathy are available that can help select the appropriate reirradiation regimen. Reirradiation of MESCC may also be performed with highly-conformal radiotherapy such as IMRT, VMAT, or SBRT. When using SBRT, a cumulative maximum EQD2 to the thecal sac ≤70 Gy_2, a maximum EQD2 of SBRT ≤25 Gy_2, a ratio ≤0.5 of thecal sac maximum EQD2 of SBRT to maximum cumulative EQD2, and a minimum interval between both courses ≥5 months are associated with a lower risk of myelopathy. Since most of the available studies are retrospective in nature, additional prospective trials are required to better define the maximum tolerated cumulative doses and doses of reirradiation. Moreover, alternative models that may be more accurate than the linear-quadratic model in calculating the BED for SBRT with higher doses per fraction need to be validated in prospective clinical studies.

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