

Excellent outcomes after radiotherapy alone for malignant spinal cord compression from myeloma

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Background. Uncertainty exists whether patients with spinal cord compression (SCC) from a highly radiosensitive tumor require decompressive spinal surgery in addition to radiotherapy (RT). This study addressed the question by evaluating patients receiving RT alone for SCC from myeloma.

Patients and methods. Data of 238 patients were retrospectively analyzed for response to RT and local control of SCC. In addition, the effect of RT on motor function (improvement, no further progression, deterioration) was evaluated. Overall response was defined as improvement or no further progression of motor dysfunction. Prior to RT, patients were presented to a neurosurgeon for evaluation whether upfront decompressive surgery was indicated (e.g. vertebral fracture or unstable spine).

Results. In the entire cohort, the overall response rate was 97% (53% improvement plus 44% no further progression). Following RT, 88% of the patients were able to walk. Of the 69 non-ambulatory patients 44 patients (64%) regained the ability to walk. Local control rates at 1, 2 and 3 years were 93%, 82% and 82%, respectively. A trend towards better local control was observed for patients who were ambulatory before starting RT ($p = 0.08$) and those with a more favorable performance status ($p = 0.07$).

Conclusions. RT alone provided excellent response rates, functional outcomes and local control in patients with SCC from myeloma. These results should be confirmed in a prospective randomized trial.

Key words: myeloma; spinal cord compression; radiotherapy alone; overall response; local control

Introduction

Myeloma patients account for about ten percent of patients presenting with malignant spinal cord compression (SCC).¹ Radiotherapy (RT) alone is the most frequently used treatment for these patients worldwide. Ten years ago, a small randomized trial of 101 patients was published that compared

RT alone to decompressive surgery plus stabilization followed by RT in highly selected patients.² In that trial the combined approach resulted in significantly better functional outcome (ambulation) and survival than irradiation alone. Therefore, upfront neurosurgery has become significantly more popular in several countries. Although patients with highly radiosensitive tumors such as myeloma,

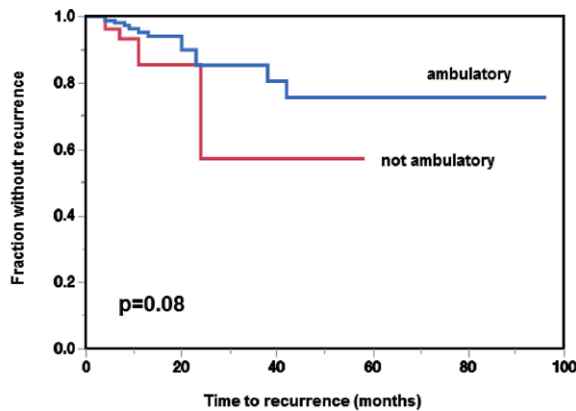


FIGURE 1. Kaplan-Meier curves of patients who were ambulatory prior to RT and of those patients who were not ambulatory.

lymphoma and germ cell tumors were excluded from the randomized trial of 101 patients, many neurosurgeons extrapolated from these findings and perform decompressive surgery in myeloma patients.² The question remains whether RT alone is sufficient or needs to be supplemented by upfront decompressive surgery in malignant SCC from a highly radiosensitive tumor. This study aims to contribute to this open question by investigating overall response and local control of SCC in patients treated with RT alone for SCC from myeloma.

Patients and methods

Data of 238 patients presenting with motor deficits of the lower extremities in consequence of SCC from vertebral body myeloma were retrospectively analyzed. Prior to the start of RT, the patients were presented to a neurosurgeon for evaluation whether upfront decompressive surgery was indi-

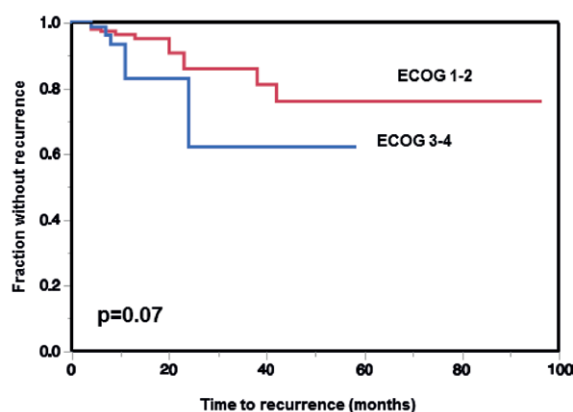


FIGURE 2. Kaplan-Meier curves of patients with an ECOG performance score of 1–2 and those patients with an ECOG performance score of 3–4.

cated, *e.g.* in case of vertebral body fracture, unstable spine or sphincter dysfunction. Patient who did not require surgery were included in this study.

RT was performed with 6–18 MV photon beams from a linear accelerator (mostly after 3D-treatment planning), and target volumes included the vertebrae affected by SCC plus on additional vertebra on either side. The study has been approved by the local ethics committee. For this retrospective study, specific written informed consent was not required.

The primary endpoint local control was defined as freedom from a symptomatic in-field recurrence of SCC in the irradiated parts of the vertebral column. In addition, the effect of radiation treatment on motor function (improvement, no further progression, deterioration) was measured. Improvement and deterioration of motor function were defined as a change of one point on a five-point scale (0 = normal strength; 1 = ambulation without aid; 2 = ambulation with aid; 3 = no ambulation; 4 = complete paraplegia).³ Patients with complete paraplegia who did not improve after RT were rated as deteriorated. Motor function at about one month (three to six weeks) following RT was compared to motor function at baseline (*i.e.* before the start of RT). Overall response to RT was defined as either improvement or no further progression of motor dysfunction.

RT was administered without upfront neurosurgery and performed either as short-course RT (1 × 8Gy, 5 × 4Gy) or longer-course RT (10 × 3Gy, 15 × 2.5Gy, 20 × 2Gy). The RT regimen plus ten other factors were analyzed for local control of SCC. The other factors included age at the time of RT (≤ 64 years *vs.* ≥ 65 years, median age: 64 years), gender, myeloma subtype (IgG subtype *vs.* other subtypes), time from first diagnosis of myeloma to SCC (≤ 15 *vs.* > 15 months), presence of extra-osseous lesions before RT (no *vs.* yes), further osseous lesions before RT (no *vs.* yes), gender, time developing motor deficits before RT (faster: ≤ 14 *vs.* slower: > 14 days), gait function before the start of RT (ambulatory *vs.* not ambulatory), number of vertebrae involved by SCC (1–2 *vs.* ≥ 3) and performance status (Eastern Cooperative Oncology Group (ECOG) performance score 1–2 *vs.* 3–4). The univariate analyses of local control of SCC were done with the Kaplan-Meier method⁴, and the Kaplan-Meier curves were compared with the log-rank test. Those factors being significant or showing a trend ($p < 0.09$) for local control were additionally analyzed in a multivariate manner with the Cox proportional hazards model.

TABLE 1. Impact of the eleven factors on local control of SCC (univariate analysis)

	At 1 year (%)	At 2 years (%)	At 3 years (%)	p-value
Age				
≤ 64 years (n = 125)	94	86	86	
≥ 65 years (n = 113)	92	75	75	0.81
Gender				
Female (n = 88)	90	78	78	
Male (n = 150)	94	85	85	0.47
Myeloma subtype				
IgG subtype (n = 153)	96	84	84	
Other subtypes (n = 85)	88	78	78	0.14
Time from myeloma diagnosis to SCC				
≤ 15 months (n = 128)	95	81	81	
> 15 months (n = 110)	91	85	85	0.83
Extra-osseous lesions				
No (n = 218)	94	82	82	
Yes (n = 20)	67	n.a.	n.a.	0.19
Further osseous lesions				
No (n = 91)	93	86	86	
Yes (n = 147)	93	76	76	0.73
Time developing motor deficits				
Faster (≤ 14 days) (n = 112)	93	81	81	
Slower (> 14 days) (n = 126)	93	83	83	0.79
Gait function before the start of RT				
Ambulatory (n = 169)	95	85	85	
Not ambulatory (n = 69)	85	57	57	0.08
Number of vertebrae involved by SCC				
1-2 (n = 112)	95	87	87	
≥ 3 (n = 126)	92	77	77	0.17
ECOG performance score				
1-2 (n = 150)	96	86	86	
3-4 (n = 88)	83	62	62	0.07
Radiotherapy regimen				
Short-course RT (n = 84)	94	69	69	
Longer-course RT (n = 154)	93	90	90	0.29
Entire cohort (n = 238)	93	82	82	

n.a. = not available

Results

Two-hundred-and-thirty-seven patients were available for evaluation of response to RT. The overall response rate at one month was 97% (230 of 237 patients); 53% of patients (n = 126) showed improvement and 44% (n = 104) no further progression. Following RT, 88% of the patients (209 of 237) were able to walk. Of 69 non-ambulatory patients 44 patients (64%) regained the ability to walk after RT.

In the entire cohort of 238 patients, the local control rates at 1, 2 and 3 years following RT of SCC were 93%, 82% and 82%, respectively. In the univariate analysis, no factor was significantly associated with local control of SCC. A trend towards better local control was observed for patients who were ambulatory before RT was started ($p = 0.08$, Figure 1) and for patients with a more favorable performance status ($p = 0.07$, Figure 2). These two factors were additionally evaluated in the multivariate analysis, where both pre-RT gait function

(risk ratio: 2.34; 95%-confidence interval: 0.80–6.10; $p = 0.11$) and performance status (risk ratio: 2.36; 95%-confidence interval: 0.85–6.09; $p = 0.09$) did not reach significance (significance = defined as $p < 0.05$).

Discussion

Malignant SCC represents a serious complication for patients with a malignant disease.^{1,5} A rapid start of treatment is required. Until 2005, radiotherapy alone has been considered the unquestioned standard treatment for SCC. In 2005, a randomized trial of 101 selected patients with SCC from different primaries, who had a good performance status and a relatively good survival prognosis, suggested that the results of RT alone can be improved by upfront decompressive surgery.² In that trial, 84% (42 of 50) of patients were able to walk after surgery plus RT compared to 57% (29 of 51) of patients

after RT alone ($p = 0.001$). The results were supported by a meta-analysis including 24 surgical series ($n = 999$) and four radiotherapy series ($n = 543$), mostly uncontrolled cohort studies.⁶ These data have led to a fundamental change of practice. In several countries, neurosurgery preceding RT has become very popular. In some centers, the majority patients with SCC receive the combined treatment rather than RT alone. This new trend includes also patients with highly radiosensitive tumors such as myeloma, although these patients were excluded from the previously mentioned randomized trial.² The question is whether these patients really need surgery in addition to RT? One should bear in mind that spinal surgery is associated with significant risks and complications such as severe wound infections. A second surgery, extensive bleeding, postoperative pneumonia, and major thromboembolic events occurred in more than 10% of patients.^{2,7,8} In addition, iatrogenic neurologic complications were reported for 9% of patients receiving surgery of the lumbar spine.⁹

In the current study, functional outcomes were excellent with a post-RT overall ambulation rate of 88% and a rate of regaining ambulatory status of 64%. Furthermore, local control of SCC achieved with RT alone was long lasting. At 3 years following RT, local control was still 82%. These excellent local control rates were achieved irrespectively of patient characteristics. None of the eleven investigated characteristics was significantly associated with local control of SCC. However, pre-RT gait function and performance status showed a trend. Three-year local control rates were 57% in initially non-ambulatory patients and 62% in patients with an ECOG performance score of 3–4, respectively. The question whether these patients would benefit from the addition of upfront decompressive surgery to RT can be properly answered only in a prospective trial. Clear indications for neurosurgery also for very radiosensitive tumors include vertebral fractures, unstable spine, sphincter dysfunction, and impairment of the spinal cord by bony fragments. According to a recent retrospective study focusing on surgery for vertebral involvement of myeloma, the probability of receiving surgery was about 40%.¹⁰ No differences in disability and quality of life were observed between patients receiving RT alone and those receiving RT plus upfront surgery. For highly selected patients, stereotactic body radiation surgery (SBRT) may also be an option.^{11,12} However, it has been recommended to use SBRT for malignant SCC only within clinical trials.¹²

In summary, in patients with malignant SCC from myeloma, RT alone provides excellent response rates, functional outcomes such as post-RT ambulation, and local control of SCC. These results should be confirmed in a prospective randomized trial.

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Interdisciplinarna soglasna izjava o indikaciji in uporabi hidrogelnega vmesnika pri radioterapiji prostate. Izkušnje pri več kot 250 bolnikih

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Izhodišča. Namen raziskave je bil doseči soglasje o indikaciji in uporabi hidrogelnega vmesnika na podlagi multicentričnih izkušenj ter posredovati uporabnikom pomembno informacijo, s katero bi skrajšali učenje te inovativne tehnike.

Metode. Interdisciplinarnega srečanja so se udeležili radioterapevti in urologi, ki so opravili 23–138 aplikacij hidrogela (SpaceOAR®) pri bolnikih z rakom prostate pred radioterapijo, kjer smo zviševali dozo. Želeli smo pridobiti praktične informacije, ki so pomembne za zaporedno injiciranje hidrogela in zdravljenje, zato smo obravnavali izkušnje uporabnikov in odgovorili na zastavljena ključna vprašanja. Pregledani smo stranske učinke, povezane s hidrogelom in ocenili delež, zdravljenje in napoved možnih tveganj.

Rezultati. Najpomembnejša indikacija za aplikacijo hidrogela je bila radioterapija z naraščajočo dozo pri histološko potrjenem raku prostate z nizkim ali vmesnim tveganjem. Priporočili smo jo pri lokalno napredovalem raku prostate. Injiciranje ali implantacijo smo opravljali pod nadzorom transrektalnega ultrazvoka in s transperinealnim pristopom po predhodni hidrodisekciji. Pri skupno 258 aplikacijah hidrogela je bil delež toksičnosti stopnje 2, ki je bila povezana z injiciranjem 2 % (n = 5). Najpogostejši zaplet (n = 4) je bilo predrtje stene rektuma, ki smo ga ugotovili ob različnih časovnih intervalih po injiciranju hidrogela in smo ga zdravili konzervativno.

Zaključki. Dosegli smo soglasje o aplikaciji hidrogelnega vmesnika. Dosedanje izkušnje kažejo, da je metoda izvedljiva, kar lahko spodbudi njeno uvedbo v več centrih. Na ta način bi lahko znižali z obsevanjem povezano gastrointestinalno toksičnost slikovno vodene radioterapije z naraščajočo dozo. Še vedno pa je možen zelo nizek delež resnih neželenih dogodkov. Zato bi morali skrbno proučiti aplikacijo in bolnika ter upoštevati možne prednosti takšnega zdravljenja.

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Odlični rezultati zdravljenja kompresije hrbtenjače pri mielomu z radioterapijo

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Izhodišča. Ni znano, ali bolniki s kompresijo hrbtenjače in radiosezibilnimi tumorji poleg radioterapije potrebujejo tudi kirurško dekompresijo hrtenjače. Zato smo v raziskavi analizirali potek bolezni pri bolnikih, ki so zboleli zaradi mielomoma in pri katerih smo ugotovili kompresijo hrbtenjače ter smo jih zdravili samo z obsevanjem.

Bolniki in metode. Retrospektivno smo analizirali podatke 238 bolnikov glede odgovora na RT in lokalno kontrolo kompresije hrbtenjače. Ocenili smo učinek radioterapije na motorično funkcijo (izboljšanje, brez nadaljnega slabšanja, poslabšanje). Odgovor smo opredelili kot izboljšanje ali odsotnost nadaljnega slabšanja motorične okvare. Pred radioterapijo smo bolnike predstavili nevrokirurgu, da je ocenil, ali je indicirana takojšnja operacija z dekompresijo (zaradi zloma vretenca, nestabilne hrbtenice).

Rezultati. V celotni kohorti je bil odgovor na radioterapijo 97 % (izboljšanje 53 %, brez nadaljnega slabšanja 44 %). Po radioterapiji je lahko hodilo 88 % bolnikov. Izmed 69 hospitaliziranih bolnikov je shodilo 44 bolnikov (64 %). Lokalna kontrola po 1, 2 in 3 letih je bila 93 %, 82 % in 82 %. Trend izboljšanja lokalne kontrole smo opazili pri bolnikih, ki smo jih obravnavali pred začetkom radioterapije oambulantno (p = 0.08), in pri tistih z boljšim stanjem zmogljivosti (p = 0.07).

Zaključki. Pri bolnikih z mielomom in kompresijo hrbtenjače zagotavlja radioterapija odličen odgovor na zdravljenje, funkcionalne rezultate in lokalno kontrolo. Rezultate bo potrebno potrditi s prospektivno randomizirano raziskavo.