Malignant extradural spinal cord compression in men with prostate cancer

Andrew Loblaw and Gunita Mitera

Department of Radiation Oncology, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

Correspondence to Dr D.A. Loblaw, 2075 Bayview Avenue, Toronto, ON M4N 3M5, Canada
Tel: +1 416 480 4806; fax: +1 416 480 6002;
e-mail: andrew.loblaw@sunnybrook.ca

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Purpose of review

Malignant epidural spinal cord compression (MESCC) is a dreaded complication of malignancy and is fortunately not common. Approximately 7% of men dying of prostate cancer will have at least one episode of MESCC during their lifetime. Treatment needs to be individualized and estimating the prognosis is critical to achieving a balance between effectiveness therapy and the burden of treatment.

Recent findings

A consortium of multiple centers has defined prognosis scales, and multiple randomized studies have helped define the optimal dose fractionation schedule for patients getting radiotherapy.

Summary

Simple prognosis scales available to assist the clinician are reviewed. For poor prognosis patients, a single fraction of 8 Gy is just as effective as multiple fractions, however, are much more convenient. For good prognosis patients, surgery and radiation should be considered. For patients not getting surgery, enrollment in clinical trials of single vs. multiple fractions of radiation should be a priority. For high-risk patients, screening strategies are being developed and hold promise for maintaining ambulation throughout the patients' lifetime.

Keywords

malignant spinal cord compression, prostate cancer, radiotherapy, surgery

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Introduction

Malignant spinal cord compression (MSCC) is one of the most dreaded complications of metastatic cancer. MSCC can be divided into intradural (intramedullary and leptomeningeal) and extradural (MESCC) [1]. Its natural history, if untreated, is usually one of relentless and progressive pain, paralysis, sensory loss, and sphincter dysfunction [2].

A population-based study of cancer patients reported that malignant epidural spinal cord compression (MESCC) is fortunately not common; between 1990 and 1995, 2.5% ($n = 3458$) of all cancer patients who died from their disease had at least one admission for MSCC [3]. The incidence of MSCC varied widely by primary cancer site, from 7.9% in patients with myeloma to 0.2% in patients with pancreatic cancer [3]. Men with prostate cancer had a 7.2% risk; however, of men dying between 40 and 60 years of age, the incidence was 17%. The chance of MESCC being the heralding symptom of prostate cancer was rare: 0.2% of all prostate cancer patients diagnosed during the study interval had MESCC at diagnosis (the average for all cancers was 0.23%).

Bayley *et al.* [4] did a study of patients with metastatic prostate cancer including patients who were castrate resistant – castration-resistant prostate cancer (CRPC). They reported that the incidence of thecal sac indentation (a surrogate of MESCC) was 32%. For patients with more than 20 metastases on bone scan and who were on androgen deprivation therapy (ADT) greater than 2 years, the risk was 44%.

Our group has published two previous evidence-based clinical practice guidelines for the diagnosis and management of MESCC in 1998 [2] and in 2005 [5]. The latter guideline was formally developed and approved through Cancer Care Ontario's Program in Evidence-Based Care (PEBC). The PEBC recommends that the guidelines be reviewed regularly and updated when potentially practice changing data have been published. Since the last guideline, several randomized control trials have been published, but to our knowledge no evidence-based guidelines have been issued.

The objective of this review was to update the literature since the last guideline, summarize the data specifically on the management of patients with metastatic prostate

who are diagnosed with MESCC. The literature search strategy employed was adopted from the initial review in 2005 [5]. When the data were available, the summary focused on prospective studies.

Prognosis

Some studies have been published to define the prognosis of patients with MESCC. In Ontario, our group showed that overall the prognosis was poor with a median survival of 2.9 months after the diagnosis of MESCC [3]. One of the strongest predictors of overall survival (OS) in our population-based study was tumor histology – nonsmall cell lung cancer had the worst median OS (1.5 months) and while myeloma had the best median OS (6.7 months). Prostate cancer had a median OS of 4 months. Note, however, that this study was conducted at a time before docetaxel [6,7], sipuleucel-T [8•], cabazitaxel [9•], and abiraterone [10•] were available. Although these therapies have been shown to improve a number of outcomes including OS, it is not clear what effect they will have on preventing or delaying the incidence of MESCC.

Other groups have showed quite a dramatic OS difference between patients able and not able to ambulate posttreatment. Maranzano *et al.* [11] documented a threefold difference in OS (10 vs. 3 months) based on the ambulatory status posttreatment. In the Italian randomized studies, patients had to have favorable histology (breast, prostate, lymphoma, seminoma, or myeloma) and no abnormal neurology to qualify for the good prognosis group (the remaining patients were considered poor prognosis) [12,13].

Rades *et al.* [14–17] have published a number of studies identifying several prognostic factors that were identified in several multivariate analyses. In a multicenter, international retrospective study of 1852 patients treated with radiotherapy, the following factors were independently prognostic: histology, visceral metastases, other bone metastases, ambulatory status before radiotherapy, interval between tumor diagnosis and MESCC, and time of developing motor deficits [15].

Rades and colleagues went on to lead the development of a prognostic scoring system based on these factors and this patient dataset. Total scores ranged between 20 and 45 points and patients were divided into five groups. The 6-month OS ranged from 4 to 99% ($P < 0.001$) with median OS estimated to range between 2 and 62 months from the worst to the best prognostic group (Tables 1 and 2). For example, an ambulatory prostate cancer with mild leg weakness, multiple bone metastases, but no visceral metastases would be considered good prognosis.

Key points

- Malignant epidural spinal cord compression is uncommon in men with metastatic prostate cancer but important to diagnose and treat early.
- The goals of the treatment are palliative, and the intensity of treatment should be guided by the patient's prognosis.
- Screening and intervening on high-risk subgroups of patients may prevent neurologic decline; however, further research is required to weigh the benefits and costs of this approach.

Surgical management of malignant epidural spinal cord compression

The strongest evidence comes from a multiinstitutional, randomized control trial by Patchell *et al.* [18] that randomized 101 patients with MRI-confirmed MESCC (cauda equina lesions excluded) to receive decompressive surgical resection with radiation 14 days later or radiation alone of 30 Gy in 10 fraction treatments. All patients were directed to receive dexamethasone 100 mg bolus and 96 mg daily (dose reduced for patients with relative contraindications to high-dose steroids). Patients were stratified by institution, tumor type, ambulatory status, and spinal stability. Thirty-eight percent of accrued patients had spinal instability.

The authors reported that patients undergoing surgery in addition to radiotherapy (30 Gy/10 fractions) were more likely to retain or maintain their ambulatory status longer compared with patients receiving radiotherapy alone (84 vs. 57%, $P = 0.001$). In addition, patients assigned to the combined modality arm experienced better ambulatory time (122 vs. 13 days, $P = 0.003$), urinary continence (74 vs. 57%, $P = 0.005$), duration of

Table 1 Prognostic score for malignant epidural spinal cord compression

Prognostic factor	Category	Score
Type of tumor	Myeloma/lymphoma	9
	Breast cancer	8
	Prostate cancer	7
	Other tumors	4
	Lung cancer	3
Other bone metastases[a]	No	8
	Yes	2
Visceral metastases[a]	No	8
	Yes	2
Tumor diagnosis to MESCC	>15 months	7
	<15 months	4
Ambulatory status pretreatment	Ambulatory	7
	Nonambulatory	3
Time to develop motor deficits before treatment	>14 days	8
	8–14 days	6
	1–7 days	3

MESCC, malignant epidural spinal cord compression. Adapted with permission [15].
[a] At the time of radiotherapy.

Table 2 Overall survival by malignant epidural spinal cord compression prognostic score

Score	6-Month OS (%)	1-year OS (%)	Median OS (months)[a]
21–25	4	0	2
26–30	11	6	5
31–35	48	23	7
36–40	87	70	25
41–45	99	89	62

MESCC, malignant epidural spinal cord compression; OS, overall survival. Adapted with permission [15].
[a] Estimated OS.

continence (median 157 vs. 17 days, $P=0.016$), and functional status (maintenance of Frankel and American Spinal Injury Association (ASIA) scores, $P=0.001$). There was a difference in survival favoring the combined modality arm (median 126 vs. 100 days, $P=0.033$).

Surgery is associated with significant morbidity that needs to be considered when deciding between surgery and radiation for medically operable patients with a single area of compression and no spinal instability or bony compression. Minimally invasive techniques may decrease the morbidity of the procedure, shorten the recovery period, and maintain the procedure's efficacy [19]. Despite this, it would be reasonable to select patients for surgery who have the longest life expectancy (groups D and E of the MESCC prognostic scale) [16].

Patients who do have surgery should have postoperative radiation of 30 Gy in 10 fractions as per the trial by Patchell *et al.* [18]. This can be started within 2 weeks of surgery.

Optimal dose fractionation schedule

The optimal dose fractionation schema should be tailored to the individual patient to optimize patient outcomes and burden of treatment.

Poor prognosis patients

Maranzano *et al.* have conducted and reported two randomized control trials addressing the question of dose fractionation schedule for poor prognosis patients. These patients were defined as all patients with poor histology tumors (melanoma or lung, sarcoma, gastrointestinal, head and neck or kidney cancers) or those good histology tumors with any functional impairment or poor performance status. It may be reasonable to extrapolate the results of these trials to the MESCC prognosis groups A, B, or C [16].

The first study, reported in 2005, randomized 300 patients 1 : 1 to a split-course of radiation (15 Gy in three fractions, 4 day break then 15 Gy in five fractions) or hypofractionated radiotherapy (8 Gy in two fractions, 1 week apart) [12]. All patients were given dexamethasone 16 mg daily during radiation, tapered off posttreatment. Patients were assessed for the ability to ambulate (with/without assistance), duration of ambulation, bladder function, OS, toxicity, and pain relief. A total of 276 patients was analyzable and the median follow-up (presumably of survivors) was 33 months. There were no significant differences in any of these outcomes (Table 3).

The Italian group's second study, reported in 2009, randomized 327 poor prognosis patients (as above) to 16 Gy in 2 fractions over 1 week vs. 8 Gy in one fraction [13]. Dexamethasone 16 mg/day was given to both groups. A total of 303 patients were analyzable; median follow-up was not reported (but appears to be approximately 5 months from the Kaplan–Meyer plots). Again, no significant differences were reported between the treatment arms for ambulation, duration of ambulation, bladder control, pain response, and OS (see Table 3). Of note, there was a nonsignificant trend towards greater in-field failures favoring the two-fraction arm in this study (2.5 vs. 6.0%, $P=0.12$).

Good prognosis patients

For patients who are ineligible for surgery and have a good prognosis for their MESCC, clinical trials are needed to determine the role of dose escalating radiation to improve outcomes.

A prospective, international nonrandomized study of 231 patients (SCORE-1 study) treated with different radiation schedules concluded that longer fractionation

Table 3 Outcomes of two randomized controlled trials by Maranzano *et al.*

	Hypofractionation study [12]		Single fraction study [13]	
Outcome	30/8 ($n=134$)	16/2 ($n=142$)	16/2 ($n=150$)	8/1 ($n=153$)
Ambulation	71%	68%	66%	62%
Duration of ambulation (med)	3.5 months	3.5 months	5 months	5 months
Bladder control	90%	89%	87%	85%
Pain response	59%	56%	53%	52%
Overall survival	4 months	4 months	4 months	4 months
Acute toxicity, Grade 3	3.7%	2.1%	–	–
In-field failure	–	–	2.5%	6%*

* $P=0.12$.

schemes were predictive of progression-free survival (PFS; 12-month PFS 72 vs. 55%, $P = 0.034$) and local control (12-month local control 77 vs. 61%, $P = 0.032$), and that the radiation schedule held up on multivariate analysis [20]. There was no relationship between the length of radiation scheme and OS or motor status post-treatment. Patients were not selected but tended to be a better prognosis group than usually reported (median OS 5 months).

In their retrospective prognostic study, Rades *et al.* [16] reported that longer fractionation schemes were associated with improved OS. Another prospective study by Rades, 40 Gy in 20 fractions did not improve functional outcomes or ambulatory status compared to 30 Gy in 10 fractions [21]. Confirmation in a prospective randomized control trial (RCT) should be done to confirm whether this is true or whether there are patient selection factors that explain the observations. In sum, there are insufficient data to support dose escalation above 8 Gy in good prognosis patients.

An international consortium of trialists is running a trial of one vs. multiple fractions of radiation (SCORAD) for all prognosis patients; patients should be entered if possible to confirm the benefit of longer vs. shorter fractionation treatments.

Screening MRI and prophylactic radiation

Several studies support the irradiation of subclinical cord compression as a method of preserving neurologic function. Predictive risk models are emerging that may help to define a population of patients at higher risk of developing cord compression [3,4,22,23], but the optimal screening strategy, population, and intervention have yet to be elucidated.

Venkitaraman *et al.* [24] reported a retrospective experience of 130 patients with CRPC in which they performed screening MRI and prophylactic radiation (SMaRT) for those patients with radiologic compression (rSCC). With this approach, the proportion of patients free from neurological deficit at 3, 6, 12, 18, and 24 months was 94, 80, 59, and 43%, respectively, in patients who had rSCC on initial MRI and 97.5, 89, 75, and 63%, respectively, in patients who had no rSCC. The authors suggested that the optimum frequency for MRI would be every 4–6 months for patients with previous squamous cell carcinoma (SCC), rapid or high prostate-specific antigen (PSA) or back pain and annually for asymptomatic patients.

A prospective clinical trial is required to confirm the value of using this approach routinely in all patients with CRPC.

Conclusion

Malignant epidural spinal cord compression is a dreaded complication of malignancy. Although more common in men with advanced prostate cancer, it is fortunately not common. The goals of treatment are palliative and the intensity of treatment should be guided by the patient's prognosis. Screening and intervening on high-risk subgroups of patients may prevent neurologic decline, but further research is needed to confirm this approach's benefit especially considering the cost and potential side-effects of this paradigm.

Acknowledgements

Conflicts of interest

None declared.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 298).

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