ELSEVIER

Radiotherapy and Oncology 74 (2005) 259–265

RADIOTHERAPY & ONCOLOGY
JOURNAL OF THE EUROPEAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY

www.elsevier.com/locate/radonline

Pre- and post-treatment daily life function in patients with hormone resistant prostate carcinoma treated with radiotherapy for spinal cord compression

Nina Aass*, Sophie D. Fosså

Department of Clinical Cancer Research, The Norwegian Radium Hospital, 0310 Oslo, Norway

Received 12 July 2004; received in revised form 30 November 2004; accepted 10 December 2004
Available online 21 December 2004

Abstract

Background and purpose: To identify prognostic factors and prospectively evaluate daily life function and pain experience in hormone resistant prostate cancer patients with spinal cord compression treated with radiotherapy.

Patients and methods: Consecutive patients treated at the Norwegian Radium Hospital from May 1996 to October 1999 participated in the study. Daily life activities were assessed at start and discontinuation of radiotherapy and 2 and 6 months thereafter using a questionnaire based on a slightly modified Barthel activity of daily living Index. The patients were followed to death. Clinical parameters (histology, extent of disease at diagnosis, time from cancer diagnosis to start of radiotherapy, time from neurological symptoms to start of radiotherapy, age, number of spinal lesions, pre-treatment function) were assessed to try to prognosticate post-treatment function.

Results: Forty-nine patients were evaluable. Time from debut of neurological deficits to start of radiotherapy was median 4 days (range 1–66). Median target dose was 30 Gy (range 9–40). Overall survival from start of radiotherapy was median 3.5 months (range 0.3–36.0). In general, improvement with regard to mobility, daily life activities and sphincter control was reported after irradiation. Post-treatment the majority of patients reported pain, usually intermittent, although they used analgesics. No clinically relevant pre-treatment parameters that predicted function after radiotherapy were identified.

Conclusions: Radiotherapy may improve mobility, daily life activity and sphincter control in patients with metastatic spinal cord compression due to hormone resistant prostate cancer. Radiotherapy should therefore be considered in all patients irrespective of the neurological deficits.

Keywords: Hormone resistant prostate cancer; Spinal cord compression; Radiotherapy; Daily life function

1. Introduction

Prostate carcinoma is the most common malignant disease in Norwegian males [3]. Skeletal metastases are frequent, and symptoms due to compression of the spinal cord and/or cauda equina are reported in 5–7% of the patients [9,12,18]. The condition represents an oncological emergency. The treatment aims first to reverse neurological deficits or at least stabilise the function and secondly to relieve pain. Although, the majority of these patients have a very limited life expectancy it is of great importance for them to maintain independence with regard to self-care. The preferred treatment for this group of patients at our institution has so far been radiotherapy as the majority of our patients have multiple metastases to the spine when referred to the hospital. Surgery has been an option for patients progressing during radiotherapy and for patients with spinal cord compression in a previously irradiated region. Irrespective of the principal local treatment all patients should receive corticosteroids immediately when compression of the spinal cord and/or cauda equina is suspected [11].

Although the optimal strategy is to start treatment of spinal cord compression before neurological deficits develop, many of the patients admitted to the Norwegian

* Corresponding author.

0167-8140/$ - see front matter © 2004 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.radonc.2004.12.001

Radium Hospital have impaired function. The present study prospectively evaluated the effect of radiotherapy on mobility and self-care as reported by patients with spinal cord compression from hormone resistant prostate carcinoma treated at our institution. Secondly, we assessed the pain experience of our patients before and after radiotherapy. We also aimed to identify predictive factors that could easily be applied in clinical practice in order to select patients who will benefit from immediate treatment and identify those whose prospects of recovery are limited.

2. Patients and methods

The Norwegian Radium Hospital (NRH) serves as a regional cancer hospital for the southern and eastern part of Norway with a population of approximately 2 million inhabitants. The majority of patients with metastatic prostate carcinoma are taken care of at the local hospitals or by general practitioners in the region. Patients in need of radiotherapy are referred to the NRH. From May 1996 to October 1999 consecutive patients hospitalised due to symptomatic epidural spinal metastases from hormone resistant prostate carcinoma were asked to participate in a prospective study. The eligibility criteria were:

1. Symptomatic spinal cord compression and/or nerve root compression due to hormone resistant metastatic prostate carcinoma. In the following both conditions are referred to as spinal cord compression for simplification.
2. Radiotherapy chosen as the principal local treatment.
3. Informed consent.

The study was approved by the regional ethics committee.

Data about the patients' history and investigations performed at diagnosis of spinal cord compression were extracted from the medical records supplemented by information from the Cancer Registry of Norway. The histology of the primary tumour was classified according to the WHO classification system [15]. The extent of the disease at diagnosis of prostate cancer was recorded as local disease, regional metastases or distant metastases according to the classification at the Cancer Registry of Norway. Patients with serum testosteron levels <3.0 nmol/l who progressed in spite of bilateral orchidectomy or treatment with LHRH analogue for more than 3 months were considered to have hormone resistant disease.

The onset of symptoms due to spinal cord compression was defined as the time when the patients first reported neurological deficits. Pain was not taken into account in this context. The diagnosis of spinal cord compression was based on clinical and radiological investigations (magnetic resonance imaging (MRI), computed tomography (CT), myelography, bone scan and/or conventional X-ray). All patients received megavoltage radiotherapy to the demonstrated intraspinal lesion(s) with margins at least covering one vertebral body proximally and distally from the lesion. The planned radiation dose was 30 Gy given in 10 fractions á 3 Gy except for patients treated to very large fields (radiation portals covering >10 vertebrae) who were to receive 40 Gy in 20 fractions á 2 Gy. All patients were observed until death.

The following parameters were looked at in patients surviving for 2 and 6 months after radiotherapy in order to try to identify parameters that could prognosticate post-treatment function with regard to mobility, urinary continence and bowel continence: Time from diagnosis of prostate cancer to start of radiotherapy (≤ 1 year versus >1 year; ≤ 2 years versus >2 years), histology (high and intermediate versus low differentiated tumours) and stage at diagnosis (locoregional disease versus distant metastases), time from symptoms of spinal cord compression to start of radiotherapy (≤ 4 days versus >4 days), age at start of radiotherapy (≤ 70 years old versus >70 years old), number of lesions causing spinal cord compression (1 lesion versus ≥ 2 lesions), pre-treatment function (vide infra).

Evaluation of the subjective effect of radiotherapy was based on responses to a questionnaire to be completed by the patients, eventually with help from a nurse or a relative. The questionnaire consisted of a slightly modified Barthel ADL (activities of daily living) Index [21]. This index monitors self-care and mobility during rehabilitation and consists of 10 items [13]. We focused on the parameters considered to be the most relevant for the patients in this specific study, and omitted the questions about bathing, sitting balance and ability to climb stairs. Furthermore, we did not focus on total ADL score, but looked at scores of individual items. In order to simplify the presentation on some occasions we dichotomised the answers into two categories: independent versus needing help/dependent; continent versus at least occasionally incontinent. In addition to the Barthel ADL Index the questionnaire also contained some ad hoc designed questions assessing the place of living, need of assistance from home care system, pain and use of analgesics. The patients were asked to complete this questionnaire immediately before start of radiotherapy and on the day of its discontinuation when still staying at the hospital. About 2 and 6 months after treatment equivalent questionnaires with a corresponding letter were mailed to the patients asking them to return the completed questionnaires by mail.

3. Statistics

In all the analyses the statistical program SPSS for PC, version 11.5, was used. The Fisher's exact test was applied for categorical variables and the Mann–Whitney *U*-test when continuous non-parametric variables were compared. Individual changes of mobility, daily life activities and sphincter control were assessed by the McNemar test.

A P-value of <0.05 was regarded as statistically significant. Overall survival calculated from start of radiotherapy was displayed by the Kaplan–Meier procedure.

4. Results

Fifty-four patients gave informed consent to participate in the investigation (Table 1). Five patients did not complete the first and the second questionnaire: Administrative error: 3 patients; unknown reason: 2 patients. Forty-nine patients with a median age of 69.1 years (range 50.6–84.6) filled in questionnaires before start of irradiation and at end of treatment. Median 2.4 months and 6.7 months after start of therapy 26 and 17 patients, respectively, also completed the questionnaires. The other patients were already dead or were terminally ill with date of death within 2 weeks of the postal sending. According to the Cancer Registry of Norway 23 patients had localised disease at the time of diagnosis, 4 had regional metastases, 18 had distant metastases whereas the extent of the disease was unknown in 4 patients. The number of patients with initially high, intermediate and low differentiated tumours was 4, 22 and 15, respectively. Eight patients did not have a biopsy at the time of diagnosis. The median time from diagnosis of prostate cancer to diagnosis of spinal cord compression was 24.7 months (range 4.7–124.3 months).

Table 1
Patient and treatment characteristics

Eligible[a]	54
Evaluable[a]	49
Age at start of radiotherapy (years)[b]	69.1 (50.6–84.6)
Time from diagnosis to onset of symptoms due to spinal cord compression (months)[b]	24.7 (4.7–124.3)
Time from onset of symptoms to admittance to local hospital (days)[b]	3 (−25–63)
Time from admittance to local hospital to referral to NRH[c] (days)[b]	2 (0–28)
Time from admittance to local hospital to admittance to NRH (days)[b]	3 (0–28)
Time from admittance to NRH to start of radiotherapy (days)[b]	1 (0–8)
Time from onset of symptoms to start of radiotherapy (days)[b]	4 (1–66)
Survival from start of radiotherapy (months)[b]	3.5 (0.3–36.0)
Diagnosis of epidural spinal cord compression based on[a]	
MRI	41
CT	6
Myelography	1
Conventional X-ray/bone scan	1
No. of lesions causing compression of spinal cord and/or nerve roots[a]	
1	31
2	13
>2	5
Dexamethasone started before admittance to NRH[a]	34
Localisation of target volume[a,d]	
Cervicothoracal spine	3
Thoracal spine	25
Thoracolumbal spine	9
Lumbal/lumbosacral spine	18
Thoracolumbosacral spine	3
Target dose (Gy)[a]	
<30	13
30	32
31–40	4
Premature termination of radiotherapy[a]	
Progressive disease	11
Perforated peptic ulcer	1
Undocumented	1

[a] No. of patients.
[b] Median (range).
[c] Norwegian Radium Hospital.
[d] Nine patients had 2 target volumes.

The diagnosis of epidural spinal metastases was based on clinical investigations and confirmed with diagnostic procedures as listed in Table 1. The majority of the patients had widespread metastases to the spine, and about two third of them had more than one epidural spinal lesion. The median time from onset of symptoms due to epidural spinal metastases to admittance at the local hospital and at the NRH is given in Table 1. In a few patients the neurological deficits occurred after admittance, thus explaining the negative minimum value of some of the ranges. In 34 of 46 patients with neurological deficits dexamethasone was started before admittance to the NRH. Radiotherapy started median 4 days (range 1–66) after onset of symptoms. The median target dose was 30 Gy (range 9–40). In 13 patients radiotherapy was prematurely stopped. Median survival from start of radiotherapy was 3.5 months (range 0.3–36.0) for all 49 patients. After 1 and 2 years eight and two patients, respectively, were still alive. Eleven patients who progressed during radiotherapy died within median 1.0 month (range 0.3–12.9) from start of treatment.

The majority of patients were staying at home before the diagnosis of epidural spinal cord compression and also at evaluation after treatment. Two months after radiotherapy about half of the patients staying at their private home were in need of assistance from the home care system whereas this was the case for only two of 13 patients at the last evaluation. Forty-six patients used analgesics before start of radiotherapy. Only one of them was without pain whereas half of the patients stated that they suffered from pain ‘often’ or ‘all the time’. At treatment discontinuation the respective figures were 7 and 5 of a total of 45 patients on painkillers. About 2 and 6 months after radiotherapy the majority of patients still used analgesics but stated that they either were without pain or only experienced intermittent pain.

At start of radiotherapy 34 patients described themselves as totally immobile whereas 35 and 30 patients, respectively, stated to be totally disabled with regard to dressing and grooming (Fig. 1). These parameters were nearly unchanged at discontinuation of irradiation when the patients were still staying at the cancer centre (data not shown). Of the 26 evaluable patients two months post-treatment eight patients

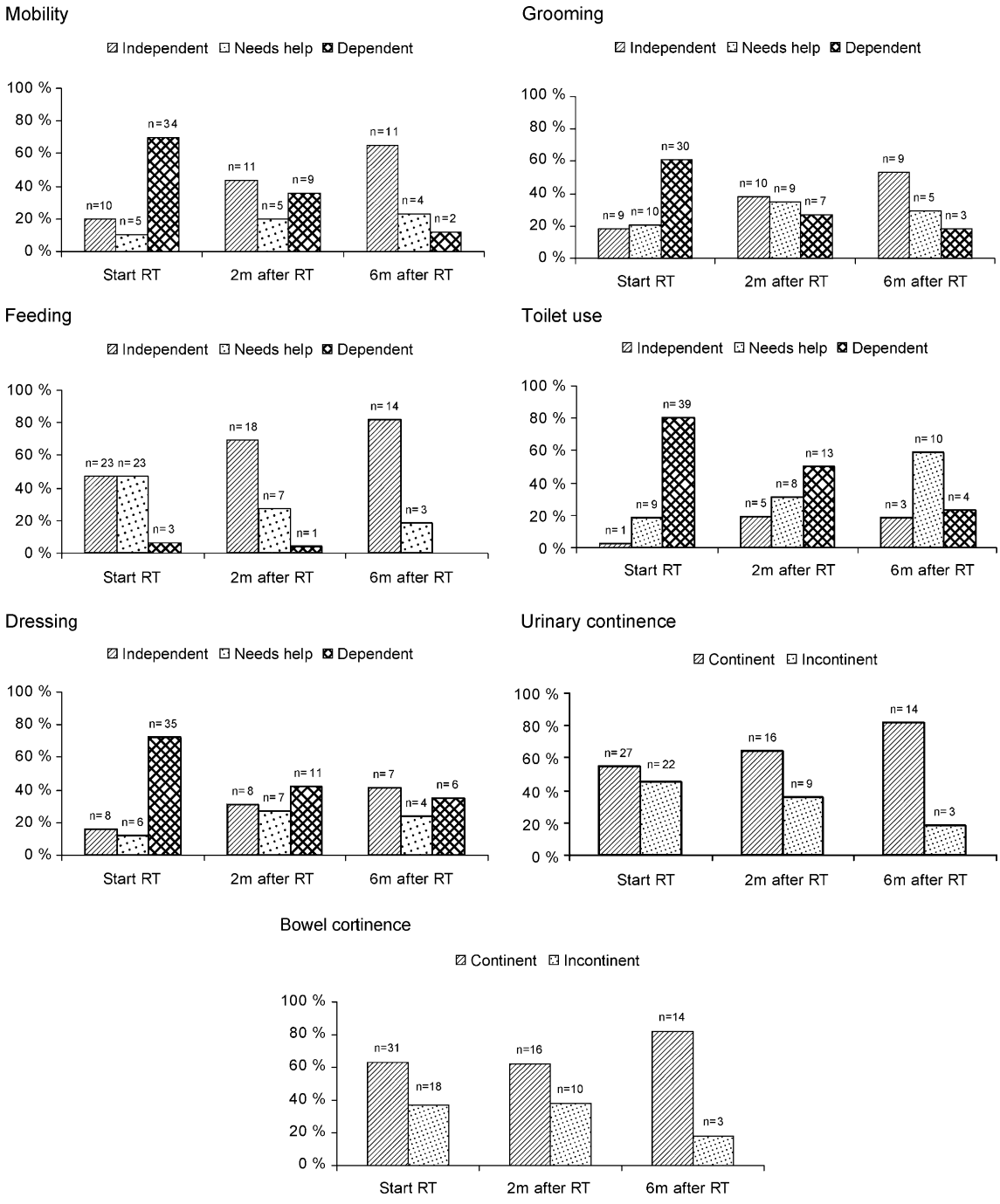

Fig. 1. Mobility, daily life activities and sphincter control in hormone resistant prostate cancer patients before and 2 and 6 months after radiotherapy due to spinal cord compression. RT, radiotherapy; m, months.

totally immobile or with reduced mobility at start of irradiation reported to be fully mobile. At the 6 months evaluation the corresponding number was seven of 17 evaluable patients. Also with regard to dressing and grooming the number of patients with regained normal function increased after therapy. Nearly half of the patients were able to eat by themselves at start of treatment. Two and 6 months after irradiation seven patients who before treatment had to be fed were able to eat by themselves. The majority of patients stated to be continent with regard to urinary and bowel function before radiotherapy. This number did not significantly change at evaluation 2 and 6 months post-treatment. With regard to toilet use most of the patients needed help or were totally independent at all times of evaluation. The majority of patients who stated to be independent before treatment remained so after irradiation irrespective of the parameter assessed.

Function (mobility, urinary and bowel continence) before start of radiotherapy did not predict function post-treatment. Significantly, more patients with distant

metastases at the initial diagnosis of the malignant disease reported normal mobility and/or urinary continence 2 months post-treatment compared to patients with locoregional disease ($P=0.001$ and 0.04, respectively). Six months after irradiation only mobility was related to extent of the disease at initial diagnosis showing significantly better results for the patients with most advanced disease ($P=0.004$). Extent of the disease at diagnosis was not related to bowel continence post-treatment. Neither histology, time from diagnosis of the malignant disease to start of radiotherapy, time from debut of neurological symptoms to start of radiotherapy, age at start of radiotherapy nor number of epidural spinal lesions were correlated with function after irradiation.

5. Discussion

In the present study, patients receiving radiotherapy due to spinal cord compression from hormone resistant prostate carcinoma were prospectively evaluated with regard to activities of daily living and experience of pain. In general, improvement in mobility, daily life activities, and sphincter control was reported after therapy. Post-treatment the majority of patients complained of pain, usually intermittent, although they used analgesics. No clinically relevant pre-treatment parameters to predict function after radiotherapy could be identified. Median survival from start of radiotherapy was only 3.5 months.

The number of cancer patients diagnosed with spinal cord compression is increasing. For some diagnostic groups this is due to improved therapy leading to prolonged survival. However, the main reasons are probably increased awareness among physicians treating cancer patients and better diagnostic tools [2]. Not all patients with occult subarachnoidal space or spinal cord compression will develop neurological deficits. On the other hand, not all patients with spinal epidural metastases do respond to treatment irrespective of how soon it is started. Therefore, it would be of great importance to be able to identify prognostic factors to differentiate those who will benefit from immediate therapy and those who will not. In the present series consecutive patients with one malignant diagnosis treated at one single institution were prospectively evaluated. To our knowledge no other studies have evaluated the effect of therapy on spinal cord compression based on the patients' own assessment of daily life function.

In order to prevent permanent sequelae due to compression of the spinal cord and/or cauda equina there is general agreement that therapy should be started as soon as possible before neurological deficits develop [1,8,14,20]. Levack et al. described symptom development until diagnosis of malignant spinal cord compression in 319 patients [10]. Pain was reported by 94% of the patients and preceded weakness, altered sensation and/or sphincter disturbances by several weeks. In our study, we did not take pain into account when symptom debut was defined as the information in the medical records about this parameter, in general, was uncertain. This means that our median time of 4 days from onset of symptoms to start of radiotherapy is a minimum value. In reality, the delay before start of definite therapy was probably much longer. Belated recognition of spinal cord compression may be due to patients' and/or doctors' delay. Information given to patients at risk and better training of health-care workers may facilitate early diagnosis of the condition. Furthermore, the availability of MRI has to be improved, as this is the investigation of choice to make an exact diagnosis of spinal cord compression.

All patients in the present study received radiotherapy as definite treatment of the spinal cord compression. Possibly, the results would have been better had surgery been performed in appropriate patients in adjunct to irradiation. In a study by Regine et al. patients with a single site of spinal cord compression from different primary tumours were randomised to either decompressive surgery plus postoperative radiotherapy or to radiotherapy alone [17]. Significantly, more patients receiving combined therapy retained their ability to walk for a longer time and also regained the ability to walk more often compared to patients treated with only irradiation. As the majority of the patients in our study had widespread metastatic disease in the spine and one third had two or more lesions causing compression of the spinal cord surgery was probably not a suitable modality for many of the patients.

Median survival from start of radiotherapy due to spinal cord compression for all patients in the present series was short. Our data are in accordance with the results in the population-based study of malignant spinal cord compression in the Ontario region [12]. They reported median survival for prostate cancer patients to be 4 months from diagnosis of spinal cord compression. This means that the event often occurs late in the course of the disease. Independent of life expectancy the restoration or preservation of daily life function as long as possible is essential in palliative oncology. For the patients' self-esteem it is of great importance to be able to care for themselves with regard to feeding, dressing, grooming and toilet use. The Barthel Index contains the activities usually considered part of any ADL assessment. It has been found to be a valid and reliable measure of disability [4]. The Index is quick and easy to answer which was important for the old patients in the present study. As the evaluation was prospective and made by the patients themselves it is more reliable than routine information taken from the medical records. In general, the patients did not report improvement with regard to mobility, daily life activities and sphincter control at the end of radiotherapy. This was probably partly due to the general restrictive routine at the hospital for care of patients with spinal cord compression. However, partly it may be related to the fact that prostate tumours often respond slowly to radiotherapy [22]. At 2 and 6 months following

discontinuation of radiotherapy there was a general improvement with regard to all parameters. Somewhat surprising was the relatively high number of patients totally disabled before start of treatment who stated to have normalised function after irradiation. This is in accordance with the fact that we were not able to identify relevant pre-treatment clinical parameters prognosticating function after therapy. When interpreting these data it is important to keep in mind that the analyses could only be performed in the rather small number of patients surviving for at least 2 months after therapy. The only parameter significantly and consistently correlated with normal mobility and sphincter control after irradiation was the presence of distant metastases at primary diagnosis of the malignant disease. This condition might result in an increased awareness among both physicians and patients of symptoms related to spinal cord compression leading to earlier diagnosis and start of therapy before development of neurological deficits. Furthermore, it cannot be ruled out that patients presenting with distant metastases have a more radiosensitive disease than patients diagnosed with locoregional disease. However, one would not omit definite treatment of spinal cord compression in a patient presenting with locoregional disease at diagnosis.

We were not able to confirm that pre-treatment ambulatory status was an important parameter predicting favourable clinical outcome as shown in other studies [1,7,8,14]. The most important reason may be that Barthel's ADL Index is not sensitive enough as it does not clearly differentiate between paralysis and paresis. Detailed information about the neurological status pre-treatment would have been helpful in this context, but unfortunately the medical records did not contain this. Furthermore, most other studies include patients with different primary tumours, probably also influencing the results. Also a few other studies have reported on paraparetic or paraplegic patients with neoplastic spinal cord compression who became ambulatory, sometimes several months after treatment discontinuation [6,19]. Thus, it is of great importance that radiotherapy is not prematurely terminated unless the patients' general condition deteriorate considerably and/or the neurological symptoms progrediate. The time elapsed from symptom debut to start of radiotherapy did not influence the functional outcome in the present series. This might be due to our definition of symptom start as we did not take pain into account as done in other studies with a much longer median time from symptom debut to start of therapy [5,10]. On the other hand, some studies have reported slow rate of symptom development to facilitate recovery [6,16].

At all times of evaluation the majority of patients stated to be in pain although most of them used analgesics. After irradiation the frequency of pain was reduced compared to the pre-treatment situation. Unfortunately, the analgesic effect of radiotherapy could not be evaluated in our study as we did not have any information about adjustment of the pain medication. However, there certainly is a need of better analgesic treatment for this group of patients as shown for other cancer patients [23].

In conclusion, radiotherapy offers the possibility of improvement with regard to mobility, daily life activities and sphincter control in patients with spinal cord compression due to hormone resistant prostate cancer, even in those who at start of treatment are totally disabled. No clinically relevant pre-treatment parameters predicting function after irradiation could be identified, and principally all patients should be offered definite local therapy.

Acknowledgements

The authors want to thank all the assistant nurses at the ward for their assistance during the study. The study was financially supported by The Norwegian Cancer Society.

References

[1] Bach F, Larsen BH, Rohde K, et al. Metastatic spinal cord compression. Occurrence, symptoms, clinical presentations and prognosis in 398 patients with spinal cord compression. Acta Neurochir (Wien.) 1990;107:37–43.
[2] Bayley A, Milosevic M, Blend R, et al. A prospective study of factors predicting clinically occult spinal cord compression in patients with metastatic prostate carcinoma. Cancer 2001;92:303–10.
[3] Cancer Registry of Norway. Cancer in Norway 2000. Report 2002.
[4] Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: a reliability study. Int Disabil Stud 1988;10:61–3.
[5] Helweg-Larsen S, Sorensen PS. Symptoms and signs in metastatic spinal cord compression: a study of progression from first symptom until diagnosis in 153 patients. Eur J Cancer 1994;30A:396–8.
[6] Helweg-Larsen S. Clinical outcome in metastatic spinal cord compression. A prospective study of 153 patients. Acta Neurol Scand 1996;94:269–75.
[7] Helweg-Larsen S, Sorensen PS, Kreiner S. Prognostic factors in metastatic spinal cord compression: a prospective study using multivariate analysis of variables influencing survival and gait function in 153 patients. Int J Radiat Oncol Biol Phys 2000;46:1163–9.
[8] Kim RY, Spencer SA, Meredith RF, et al. Extradural spinal cord compression: analysis of factors determining functional prognosis—prospective study. Radiology 1990;176:279–82.
[9] Kuban DA, el Mahdi AM, Sigfred SV, Schellhammer PF, Babb TJ. Characteristics of spinal cord compression in adenocarcinoma of prostate. Urology 1986;28:364–9.
[10] Levack P, Graham J, Collie D, et al. Don't wait for a sensory level—listen to the symptoms: a prospective audit of the delays in diagnosis of malignant cord compression. Clin Oncol (R Coll Radiol) 2002;14:472–80.
[11] Loblaw DA, Laperriere NJ. Emergency treatment of malignant extradural spinal cord compression: an evidence-based guideline. J Clin Oncol 1998;16:1613–24.
[12] Loblaw DA, Laperriere NJ, Mackillop WJ. A population-based study of malignant spinal cord compression in Ontario. Clin Oncol 2003;15:211–7.
[13] Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. Md State Med J 1965;14:61–5.

[14] Maranzano E, Latini P. Effectiveness of radiation therapy without surgery in metastatic spinal cord compression: final results from a prospective trial. Int J Radiat Oncol Biol Phys 1995;32:959–67.
[15] Mostofi FK, Sesterhenn I, Sobin LH. Histological typing of prostate tumors. International classification of tumors. World Health Organization; 1980.
[16] Rades D, Heidenreich F, Karstens JH. Final results of a prospective study of the prognostic value of the time to develop motor deficits before irradiation in metastatic spinal cord compression. Int J Radiat Oncol Biol Phys 2002;53:975–9.
[17] Regine WF, Tibbs PA, Young A. Metastatic spinal cord compression: a randomized trial of direct decompressive surgical resection plus radiotherapy vs. radiotherapy alone. Int J Radiat Oncol Biol Phys 2003;57:125.
[18] Rosenthal MA, Rosen D, Raghavan D, et al. Spinal cord compression in prostate cancer. A 10-year experience. Br J Urol 1992;69:530–3.
[19] Smith EM, Hampel N, Ruff RL, Bodner DR, Resnick MI. Spinal cord compression secondary to prostate carcinoma: treatment and prognosis. J Urol 1993;149:330–3.
[20] Turner S, Marosszeky B, Timms I, Boyages J. Malignant spinal cord compression: a prospective evaluation. Int J Radiat Oncol Biol Phys 1993;26:141–6.
[21] Wade DT, Collin C. The Barthel ADL Index: a standard measure of physical disability? Int Disabil Stud 1988;10:64–7.
[22] Wang JZ, Guerrero M, Li XA. How low is the alpha/beta ratio for prostate cancer? Int J Radiat Oncol Biol Phys 2003;55:194–203.
[23] Zhukovsky DS, Gorowski E, Hausdorff J, Napolitano B, Lesser M. Unmet analgesic needs in cancer patients. J Pain Symptom Manage 1995;10:113–9.