Case Reports in Oncology

Case Rep Oncol 2012;5:444–448
DOI: 10.1159/000341874

Published online:
August 15, 2012

ISSN 1662–6575
www.karger.com/cro

Neurological Adverse Effects after Radiation Therapy for Stage II Seminoma

Liv Ebbeskov Lauritsen Peter Meidahl Petersen
Gedske Daugaard

Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Key Words
Plexopathy · Myelopathy · Radiation therapy · Testicular cancer · Radiation adverse effects

Abstract
We report 3 cases of patients with testicular cancer and stage II seminoma who developed neurological symptoms with bilateral leg weakness about 4 to 9 months after radiation therapy (RT). They all received RT to the para-aortic lymph nodes with a total dose of 40 Gy (36 Gy + 4 Gy as a boost against the tumour bed) with a conventional fractionation of 2 Gy/day, 5 days per week. RT was applied as hockey-stick portals, also called L-fields. In 2 cases, the symptoms fully resolved. Therapeutic irradiation can cause significant injury to the peripheral nerves of the lumbosacral plexus and/or to the spinal cord. RT is believed to produce plexus injury by both direct toxic effects and secondary microinfarction of the nerves, but the exact pathophysiology of RT-induced injury is unclear. Since reported studies of radiation-induced neurological adverse effects are limited, it is difficult to estimate their frequency and outcome. The treatment of neurological symptoms due to RT is symptomatic.

Introduction

Radiation therapy (RT) is the standard treatment in clinical stage (CS) IIA/B seminoma. Total doses of around 30 Gy in CS IIA and 36 Gy in CS IIB have been standard in many centres. With modern radiation techniques, this treatment results in a relapse-free survival of 6 years for 95% of the stage IIA patients and for 89% of the stage IIB patients. Overall survival is close to 100%. The target volume includes the para-aortal and ipsilateral iliac lymphatics. In CS IIB, the lateral field margins are individually modified according to the extension of the lymph nodes with a safety margin of 1.0–1.5 cm [1].

Gedske Daugaard

Department of Oncology 5073, Rigshospitalet
University of Copenhagen
Blegdamsvej 9, DK–2100 Copenhagen (Denmark)
Tel. +45 3545 4677, E-Mail gedske.daugaard@rh.regionh.dk

Case Rep Oncol 2012;5:444–448
DOI: 10.1159/000341874
Published online: August 15, 2012

ISSN 1662–6575
www.karger.com/cro

Therapeutic irradiation can cause significant injury to any part of the nervous system; in rare cases also to the lumbosacral plexus [2]. The lumbosacral plexus represents the nerve supply to the pelvis and lower limbs. It is formed by the nerve roots of L1–L4 and L5–S5 [3, 4].

After receiving pelvic irradiation, the patients may develop progressive leg weakness (often bilateral) dysesthesias and numbness. Pain generally develops later. Weakness may involve any muscle innervated by L2–S1, but often has a L5–S1 predominance. Therefore, involvement of the anal and/or urethral sphincters and sensory supply to the perineum is rarely seen [5].

We report 3 cases with neurological symptoms/adverse effects in men with testicular cancer receiving RT to the para-aortic lymph nodes to bring awareness of this rare and grave side effect of RT. The patients all received a total dose of 40 Gy (36 Gy + 4 Gy as a boost against the tumour bed) with a conventional fractionation of 2 Gy/day, 5 days per week.

None of our patients was or had been treated with chemotherapy, and no predisposing factors such as alcohol abuse, hypertension or diabetes were reported.

Case Reports

Patient A

Patient A was a 33-year-old male diagnosed with a seminoma in the left testicle in December 2003. Due to a para-aortic lymph node 16 mm in size, with a seminoma verified by a biopsy, the patient was referred for infradiaphragmatic RT. The treatment started in March 2004 and ended 1 month later. Four months after RT, the patient developed bilateral leg weakness. There were no dysesthesias or lack of function of the anal or urethral sphincter.

Progression of the patient's testicular cancer was ruled out. Magnetic resonance imaging (MRI) was without signs of spinal cord or cauda equina affection or tumour relapse, but showed radiation sequeale in the spinal bone from Th11, Th12 to os sacrum. Motoric evoked potentials were normal and an electromyogram showed non-specific abnormalities in the muscles of the leg (the right peroneus longus, left tibialis anterior and right vastus medialis). This is neither diagnostic for radiation-induced plexo- or myelopathy, nor can it rule out the diagnosis.

In an attempt to ease the patient's symptoms, he was administered the steroid prednisolone (75 mg/day) and treatment with hyperbaric oxygen 2 h/day for 30 days was started. In December 2004, the patient was able to walk, run and ride a bike, but in February 2005, the leg weakness returned and treatment with hyperbaric oxygen was repeated. Unfortunately, this second treatment showed no effect and was stopped after 20 days. The patient also underwent physiotherapy for several months. One year later, he was still suffering from paralysis of the nervus peroneus of the right foot.

Patient B

Patient B was a 36-year-old male diagnosed with seminoma in the left testicle in March 1999. A routine CT scan in October 2003 showed growth of a para-aortic lymph node and a biopsy revealed a seminoma. The patient underwent RT from February to March 2004. Four months after RT, he developed bilateral leg weakness. Due to progression, the patient was unable to walk and had to use a wheelchair. A CT scan showed no signs of relapse. After assessment by a specialist in neurology, the patient started treatment with hyperbaric oxygen, steroids (prednisolone 75 mg ×1) and physiotherapy for several months. Six months after onset of the neurological symptoms, he was able to walk short distances without crutches and to ride a bike. After 8 months, he was able to walk longer distances. In 2007, 36 months after RT, the patient had fully recovered.

Case Rep Oncol 2012;5:444–448
DOI: 10.1159/000341874
Published online: August 15, 2012

ISSN 1662–6575
www.karger.com/cro

Patient C

Patient C was a 30-year-old male diagnosed with seminoma in the left testicle in September 2004. A CT scan showed an enlarged para-aoritic lymph node. The patient underwent RT in November 2004, and in August 2005, he developed neurological symptoms with bilateral leg weakness. An MRI showed affection of the cauda equina and it was concluded that this was caused by radiation. The patient underwent the same treatment as the 2 patients reported above. Forty-two months after RT, the patient's neurological symptoms had resolved.

All 3 cases presented themselves within a period of a few months from each other. We have had no cases of neurological adverse effects within the last 15 years except the cases described here.

Radiation Treatment

RT was applied as hockey-stick portals, also called L-fields, through ventrodorsal opposing fields covering macroscopically enlarged lymph nodes together with retrocrural, para-aortic and ipsilateral high iliac, external iliac and obtural lymph nodes as assessed by CT scans with a 1–1.5-cm safety margin. The upper border of the field was posed at the cranial rim of the eleventh thoracic vertebra and the lower field margin was 1 cm below the obtural foramen. The caudal part of the L covered the presacral and ipsilateral iliac nodes. The para-aortic and iliac regions were treated in one field. Irradiation was performed with 6- to 18-MV photons of linear accelerators. The dose plans were carefully re-examined and disclosed no dosimetric irregularities in any of the above-mentioned cases. The overall maximum dose was between 104–108%. The dose administered to macroscopically enlarged nodes was 2 Gy × 20, and the dose administered to the remaining field was 2 Gy × 18.

Discussion

We presented 3 patients with severe neurological adverse effects after RT for stage II seminoma**.** The diagnosis of radiation-induced plexopathy/myeolopathy in the cases discussed was supported by the lack of active locoregional relapse visible on a CT scan. MRI can also be helpful in resolving the reasons for unspecific neurological symptoms in the lower extremities as radiation-induced plexopathy does not produce nerve enhancement on MRIs, but an increase in T_2-weigthed signal may occur. Electromyograms are often without any specific abnormalities.

RT is believed to produce plexus injury by both direct toxic effects and secondary microinfarction of the nerves, but the exact mechanism of RT-induced injury is unclear. With a dose above 1 Gy, changes can be observed in Schwann cells, fibroblasts, vascular- and perineural cells. Injury may occur after external beam photon therapy, interstitial or intracavitary radiation implants or combined photon and proton beam RT [2]. The effect seems to be dose dependent. In animal experiments, a threshold dose of 20–25 Gy has been noted [6]. Radiation doses, in our cases, did not exceed the predicted tolerance for peripheral nerves, and accumulated doses below 40 Gy with a conventional fractionation of 1.8–2.0 Gy/day are considered to have a low risk for late adverse effects on the nervous system [7].

In a trial designed to compare the efficiency and the acute and long-term morbidity of adjuvant RT (30 Gy in 15 fractions vs. 20 Gy in 10 fractions) in patients with stage I

Case Rep Oncol 2012;5:444–448
DOI: 10.1159/000341874
Published online: August 15, 2012

ISSN 1662–6575
www.karger.com/cro

seminoma, it was concluded that 20 Gy in 10 daily fractions for 2 weeks reduced acute morbidity [8].

Differential diagnoses related to unspecific neurological symptoms in the lower extremities can be spinal cord compression, neoplastic meningitis, primary plexus tumours, neurotoxicity related to chemotherapy, paraneoplastic plexopathy and postinfectious plexopathy [9]. These conditions may also coexist in the same patient. Normally, 98% of the patients with neoplastic plexopathy feel pain, the sensory symptoms often occur later than they do in radiation-induced plexopathy and the symptoms are usually unilateral. None of these differential diagnoses were likely in the cases presented.

In a study by Brydoy et al. [5], 11 men (3.2%) with testicular cancer had neurological symptoms probably related to RT. Seven were treated with 25.2–36 Gy and presented with sensory symptoms about 2 months after RT. These symptoms resolved after 1–3 months in all but 1 patient. The remaining 4 men (dose 36–40 Gy) had motor impairment which lasted at least 1 year. None had persistent pareses at the long-term follow-up. There was a statistically significant increase in the presence of motor symptoms with higher doses [5].

Two cases were reported by Dahele et al. [10], 1 with rectal adenocarcinoma and 1 with squamous carcinoma of the anal canal, who developed bilateral weakness of the legs 5 and 4 months after RT, respectively. Improvement was seen after several months [10]. They were treated with pelvic radiation at a dose of 45 Gy and with two-phase radical chemoradiation at 27.5 Gy x 2, respectively. Frykholm et al. [7] described subacute radiation-induced lumbosacral plexopathy in 6 patients with rectal adenocarcinoma during or after preoperative RT. In 4 of the 6 patients, neurological symptoms resolved over a period of 5 months to 6 years. Two patients had persisting neurological problems [7].

In patients with gynaecological malignancies, a slow progression of neurological symptoms followed by the stabilisation of the symptoms is often observed, but not recovery [11, 12]. Radiation myelopathy has been observed after 5 to 13 months in patients receiving stereotactic body RT [13].

The treatment of neurological symptoms is symptomatic. Hyperbaric oxygen has been used relatively frequently, even though there is no level 1 or 2 evidence concerning benefit of this treatment. Due to the limited number of cases with radiation-induced neurological adverse effects, it is difficult to estimate their frequency and outcome. In general, the recommended treatment is the best supportive care [4].

Case Rep Oncol 2012;5:444–448
DOI: 10.1159/000341874
Published online: August 15, 2012

ISSN 1662–6575
www.karger.com/cro

References

1 Classen J, Schmidberger H, Meisner C, Souchon R, Sautter-Bihl ML, Sauer R, Weinknecht S, Kohrmann KU, Bamberg M: Radiotherapy for stages IIA/B testicular seminoma: final report of a prospective multicenter clinical trial. J Clin Oncol 2003;21:1101–1106.

2 Dropcho EJ: Neurotoxicity of radiation therapy. Neurol Clin 2010;28:217–234.

3 Planner AC, Donaghy M, Moore NR: Causes of lumbosacral plexopathy. Clin Radiol 2006;61:987–995.

4 Jaeckle KA: Neurologic manifestations of neoplastic and radiation-induced plexopathies. Semin Neurol 2010;30:254–262.

5 Brydoy M, Storstein A, Dahl O: Transient neurological adverse effects following low dose radiation therapy for early stage testicular seminoma. Radiother Oncol 2007;82:137–144.

6 Vujaskovic Z, Gillette SM, Powers BE, LaRue SM, Gillette EL, Borak TB, Scott RJ, Colacchio TA: Intraoperative radiation (IORT) injury to sciatic nerve in a large animal model. Radiother Oncol 1994;30:133–139.

7 Frykholm GJ, Sintorn K, Montelius A, Jung B, Pahlman L, Glimelius B: Acute lumbosacral plexopathy during and after preoperative radiotherapy of rectal adenocarcinoma. Radiother Oncol 1996;38:121–130.

8 Jones WG, Fossa SD, Mead GM, Roberts JT, Sokal M, Horwich A, Stenning SP: Randomized trial of 30 versus 20 Gy in the adjuvant treatment of stage I testicular seminoma: a report on Medical Research Council Trial TE18, European Organisation for the Research and Treatment of Cancer Trial 30942 (ISRCTN18525328). J Clin Oncol 2005;23:1200–1208.

9 Chad DA, Bradley WG: Lumbosacral plexopathy. Semin Neurol 1987;7:97–107.

10 Dahele M, Davey P, Reingold S, Shun Wong C: Radiation-induced lumbosacral plexopathy: an important enigma. Clin Oncol (R Coll Radiol) 2006;18:427–428.

11 Georgiou A, Grigsby PW, Perez CA: Radiation induced lumbosacral plexopathy in gynaecologic tumors: clinical findings and dosimetric analysis. Int J Radiat Oncol Biol Phys 1993;26:479–482

12 Enevoldson TP, Scadding JW, Rustin GJS, Senanayake LFN: Spontaneous resolution of a postirradiation lumbosacral plexopathy. Neurology 1992;42:2224–2225.

13 Sahagl A, Ma L, Gibbs I, Gerszten PC, Ryu S, Soltys S, Weinberg V, Wong S, Chang E, Fowler J, Larson DA: Spinal cord tolerance for stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 2010;77:548–553.