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Case Report Open Access

Scylla or Charybdis: Case Report on Radiation Tolerance of the Spinalcord

Astrid Dalhaug[1], Adam Pawinski[1], Terje Tollåli[2] and Carsten Nieder[1,3]*

[1]Department of Oncology and Palliative Medicine, Nordland Hospital, Bodø, Norway
[2]Department of Internal Medicine, Nordland Hospital, Bodø, Norway
[3]Faculty of Health Sciences, Institute of Clinical Medicine, University of Tromsø, Tromsø, Norway

Abstract

A case of rapid cancer progression causing impending spinal cord compression at the margin of a previously irradiated treatment volume close to the thoracic spinal cord in a patient with non-small cell lung cancer is presented. The patient and treating physicians were faced with a difficult decision. Either reirradiate and accept a considerable risk of delayed radiation myelopathy or risk paraplegia as a result of tumour progression. To prevent rapid development of neurological deficits, the patient was reirradiated only 34 days after he had finished his initial course of simultaneous radio- and chemotherapy. The high cumulative spinal cord dose (corresponding to 84 Gy in 2-Gy fractions) and short interval to reirradiation resulted in a high risk of radiation myelopathy according to a previously published risk score. However, no treatment-related toxicity developed and neurological function was preserved for almost 5 months. Eventually, tumour progression resulted in paraplegia. This case illustrates important issues around palliative reirradiation of target volumes close to the spinal cord.

Keywords: Non-small cell lung cancer; Bone metastases; Metastatic spinal cord compression; Radiotherapy; Spinal cord; Radiation myelopathy

Background

Metastatic spinal cord compression continues to represent a challenging situation in oncology [1,2]. Primary or locally recurrent tumours might also threaten the neurological function if they are located close to the spinal cord. If tumours arising in previously irradiated regions invade the spinal canal, the radiation tolerance of the spinal cord might seriously limit further radiation treatment [3]. The present case illustrates important aspects around reirradiation options.

Case presentation

A 67-year-old male presented to his pulmologist with constant pain in the right posterior hemithorax 4 months after he had undergone lobectomy of the right lower lobe. This procedure had been performed because of poorly differentiated squamous cell carcinoma, maximum diameter 7cm, stage IIB (T3 N0 M0), as shown in (Figure 1). The only abnormal haematology or blood chemistry value before surgery was thrombocytosis (593 x 10^9/l, reference value 130-400).

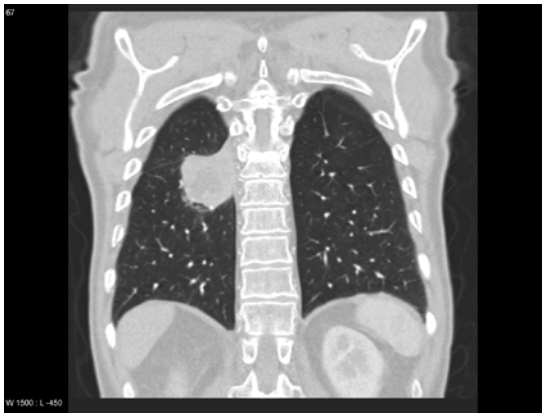

Figure 1: Preoperative computed tomography imaging showing T3 squamous cell carcinoma of the right lung.

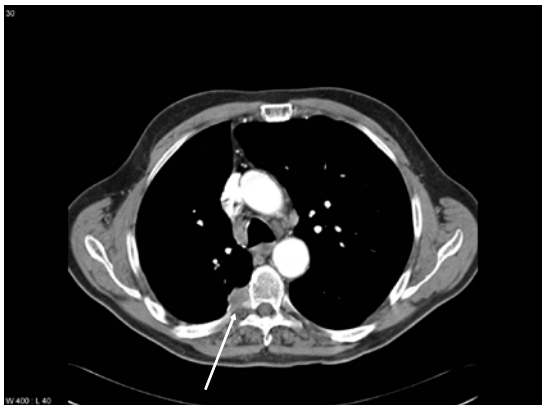

Figure 2: Computed tomography scan of the chest showing paravertebral tumour relapse after lobectomy (white arrow). Status before simultaneous radio- and chemotherapy.

The patient had declined adjuvant chemotherapy. His medical history was unremarkable (no comorbidity or medication). He had stopped smoking before thoracic surgery. Diagnostic imaging with chest computed tomography (CT) scan revealed local relapse with infiltration of the thoracic wall (Figure 2). No lymph node or distant metastases were detected. The patient received simultaneous radio- and chemotherapy (3-D conformal radiotherapy, 4 coplanar fields, dose per fraction 1.8 Gy, total dose 59.4 Gy, no inclusion of regional lymph nodes). Carboplatinum was given on day 1, 22 and 43 (AUC 3,

***Corresponding author:** Carsten Nieder, Department of Oncology and Palliative Medicine, Nordland Hospital, 8092 Bodø, Norway, Tel: +47 75 57 8449; Fax: +47 75 53 4975; E-mail: carsten.nieder@nlsh.no

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Calvert formula), Vinorelbin on day 1, 8, 22, 29, 43 and 50 (30 mg/m^2). At that time, the patient had persistent thrombocytosis. Haemoglobin was 12.8 g/dl (reference value 13.4-17.0). His performance status was good (Eastern Cooperative Oncology Group status 1), no history of weight loss >5%. During radiochemotherapy, haemoglobin decreased to 10.8 g/dl. No other toxicities were observed.

Four weeks after the last radiation treatment the patient complained about increasing pain. New CT scans revealed stable disease in the treated area, 2 small ipsilateral lung metastases and a large paravertebral mass invading the 8. and 9. Thoracic vertebra and causing impending spinal cord compression (Figure 3). The patient had no neurological deficit, unchanged performance status and slight elevation of serum alkaline phosphatase (111 U/l, reference value <105). After discussion of neurosurgical treatment options, the decision was made to proceed with palliative radiotherapy in spite of the fact that parts of the 7. and 8. thoracic vertebra were included in the previous planning target volume. The dose-limiting normal tissue in this area was the spinal cord, which had received a maximum of 87% of the prescription dose, i.e. 33 fractions of 1.57 Gy, though not to the complete cross-section (Figure 4). According to the linear-quadratic model, this dose is equivalent to 46 Gy in 2-Gy fractions (α/β-value 2 Gy, biologically equivalent dose 92 Gy_2) [4]. The following formula might be used to calculate the equivalent dose. BED = n • d • (1+d ÷ α/β), where n = number of fractions and d = dose per fraction. One of the commonly used regimens of palliative radiotherapy for metastatic

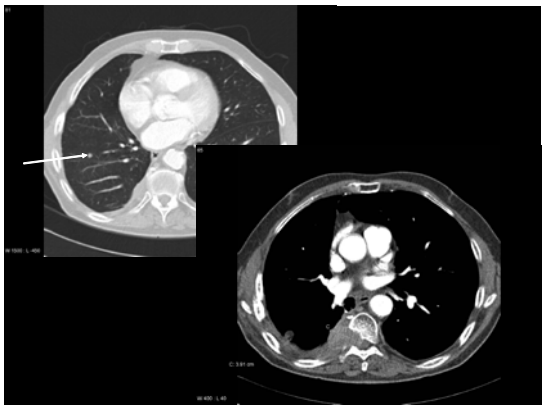

Figure 3: Computed tomography scan after radio- and chemotherapy showing marginal relapse. The tumour causes destruction of a vertebral body and impending spinal cord compression. The white arrow in the upper left hand corner indicates a newly diagnosed lung metastasis.

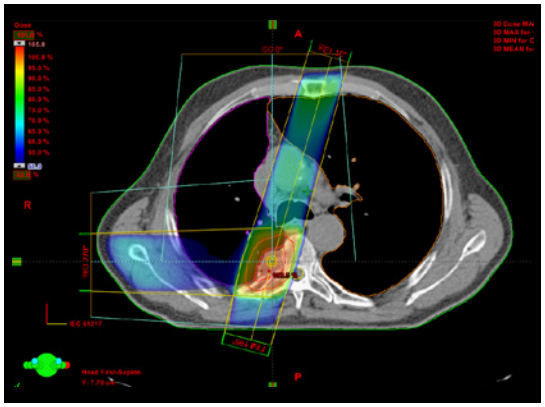

Figure 4: Treatment planning CT scan showing the dose distribution during initial radio- and chemotherapy (total dose to the ICRU reference point 59.4 Gy, dose per fraction 1.8 Gy). Clinical target volume and planning target volume are displayed. They received at least 95% of the reference dose. The treatment planning system was Eclipse by Varian Inc.

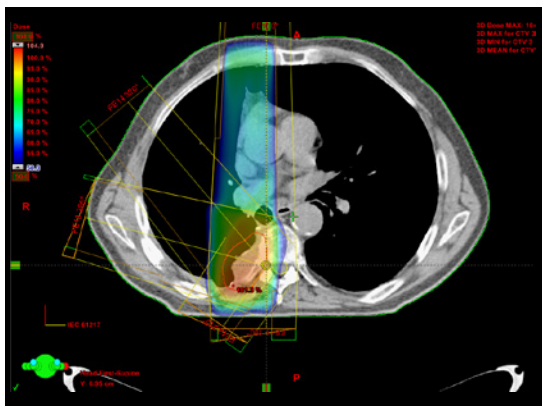

Figure 5: Treatment planning CT scan showing the dose to the reirradiated spinal cord at the level of the 8. thoracic vertebra (total dose to the ICRU reference point 30 Gy, dose per fraction 3 Gy). The maximum dose to the spinal cord equalled 98% of the reference dose. The lowest dose level displayed here is the 50% isodose. The treatment planning system was Eclipse by Varian Inc.

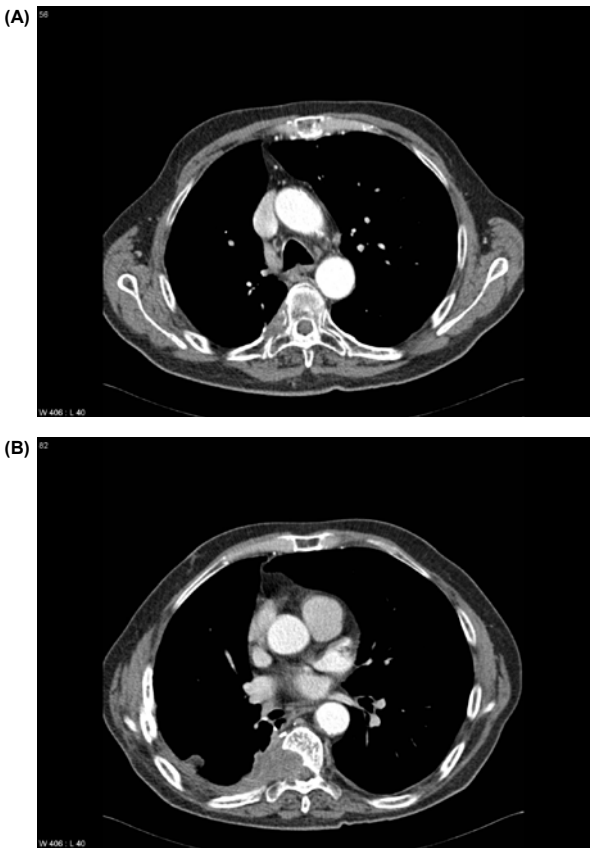

Figure 6: Computed tomography scans after reirradiation. A: The initially treated tumour, status after 59.4 Gy plus chemotherapy (slight shrinkage not fulfilling the RECIST criteria of partial remission). B: The tumour which received 30 Gy in 10 fractions of 3 Gy (classified as stable disease).

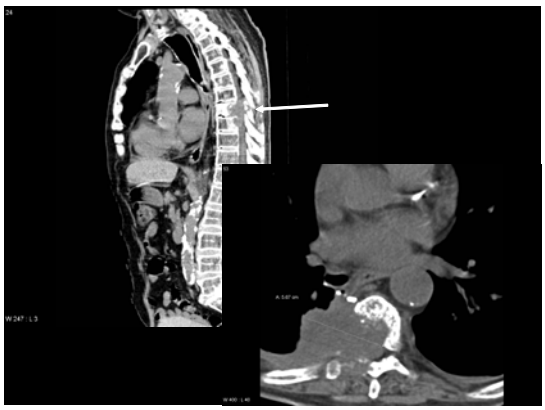

Figure 7: Computed tomography scans 5 months after reirradiation. Local progression resulting in spinal cord compression and paraplegia.

spinal cord compression consists of 10 fractions of 3 Gy. This regimen can also be used in a variety of other palliative scenarios and was chosen for this patient. We calculated a 3-D conformal treatment plan which resulted in a maximum spinal cord dose of 98% of the prescribed dose (given to 0.4 cm^3 of the spinal cord, Figure 5), resulting in a biologically equivalent dose of 75 Gy_2 (α/β-value 2 Gy). Thus the cumulative maximum spinal cord dose to this small volume equalled 92 + 75 = 167 Gy_2 (equivalent to 84 Gy in 2-Gy fractions). The cumulative dose to 1 cm^3 of the spinal cord was equivalent to 64 Gy in 2-Gy fractions. The length of the overlap was 2.1 cm. We used our previously published risk score to estimate the risk of radiation myelopathy as a consequence of reirradiation to the spinal cord [5,6]. The score is based on cumulative biologically equivalent dose, interval between the series, and high biologically equivalent dose of either initial or subsequent radiotherapy (≥102 Gy_2). Regarding cumulative biologically equivalent dose (167 Gy_2) the patient scored 5 points. The interval between the last radiation fraction of the initial course and the first fraction of the second course was 34 days, i.e. shorter than the cut-off value of 6 months. Therefore, 4.5 points had to be added to the score. This resulted in a final score of 9.5 points. With a score of 9.5 points, the patient belonged to the high risk group (>6 points). In our previous publication, nine out of ten patients with high risk developed radiation myelopathy.

In order to explore systemic treatment options (epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors) in this case of squamous cell non-small cell lung cancer (NSCLC), the primary tumour was examined for the presence of mutations in exon 18-21 of the EGFR gene, but no such mutation was detected. Therefore, chemotherapy with paclitaxel was chosen (dose 90 mg/m^2). The first cycle started 12 days after completion of reirradiation. The patient also started with zoledronic acid 4 mg every 4 weeks. At the start of chemotherapy, CT showed slight regression in both irradiated areas (less than partial remission), no new metastases were detected (Figure 6 A and B). After 3 cycles, the patient refused further treatment because of grade III neuropathy. No haematological toxicity was observed. Two months later, all lesions were unchanged in size. Another six weeks later, i.e. almost 5 months after reirradiation, the patient collapsed and was hospitalised. CT showed no signs of brain metastases, but local progression in both irradiated areas with considerable spinal cord compression (Figure 7). Neurological examination revealed complete paralysis of both lower extremities. No further oncological treatment was administered. The patient developed increasing cachexia and died approximately 2 months later. Survival was 14.4 months from lobectomy and 6.7 months from reirradiation.

Conclusions

This case illustrates therapeutic challenges which might arise when tumours recur at the margin of a previously irradiated target volume. If inoperable, the tolerance of critical normal tissues might seriously limit further treatment [7]. Initially, i.e. for post-surgical relapse, combined radio- and chemotherapy was administered. One of several platinum-based doublet regimens was chosen. Others would have been possible, but it appears doubtful whether a better response could have been obtained. During initial radio- and chemotherapy a generally accepted, conservative dose limit to the spinal cord was respected (46 Gy in 2-Gy fractions) [8]. Marginal recurrence developed shortly after completion of the initial treatment course. Even retrospectively, the new tumour invading the spinal canal was not visible on the initial diagnostic and treatment planning CT scans. This rapid growth and the fact that the tumour already threatened the spinal cord made the treating physicians believe that neurological deficits would develop in less than 2-3 weeks. It was clear that reirradiation would expose parts of the spinal cord at the level of the 7. and 8. thoracic vertebra to considerable cumulative radiation doses (overlap 2.1 cm), because no healthy tissue separated the cord from the tumour. However, neurosurgery was not considered an option. It has to be emphasized that such cases must be presented to a neurosurgeon before proceeding with other treatments. After deciding that radiotherapy would be the preferred approach, dose and fractionation had to be considered. Recently, hypo fractionated stereotactic body radiotherapy to spinal target volumes has been introduced [9-11]. This approach allows for very precise administration of fractionated or single fraction treatment with steep dose gradients. However, the typical dose per fraction is quite high and this might result in an unfavourable therapeutic ratio for the previously irradiated spinal cord [12]. Moreover, small geographical errors (set-up errors) might result in administration of higher doses than anticipated. It was felt that an approach with lower doses per fraction would result in a better therapeutic ratio. In principle, the stereotactic technique (or frameless image-guided approaches) can also be used to administer conventionally fractionated or moderately hypofractionated regimens. However, such treatment was not available in the part of Norway covered by our regional health authority (Helse Nord) and the hospitals belonging to other health authorities were such technology was available had long waiting lists and did not prioritize palliative reirradiation. Therefore, we had to rely on conventional technology. We did not expect the cancer cells to be highly radiosensitive as the response after 59.4 Gy plus concomitant chemotherapy was quite disappointing in spite of the limited volume of the irradiated tumour. Therefore, short course low-dose radiotherapy, e.g. 20 Gy in 5 fractions [1], was not an attractive option. We also felt that the rapid development of lung metastases might indicate a limited survival expectation. This argued against protracted schedules such as 40 Gy in 20 fractions. Therefore, we chose 30 Gy in 10 fractions followed by full-dose systemic therapy with paclitaxel. More aggressive systemic treatment might have been possible, but the patient was reluctant to accept serious side effects and had already opted against adjuvant chemotherapy after lobectomy. He also decided to discontinue paclitaxel chemotherapy after development of neuropathy.

For the reirradiation regimen of 30 Gy in 10 fractions, we evaluated the risk of radiation myelopathy as previously described [5,6]. Based on animal experiments, no recovery from sublethal damage can be expected only 1-2 months after the initial treatment [13]. In the present case both short interval and high cumulative radiation dose contributed to the risk of myelopathy. The third risk factor, high biologically equivalent dose of one of the two treatment series, was

absent. The risk score indicated that the present patient belonged to the high risk group. In this group, 9 out of 10 previously published patients developed radiation myelopathy. In some instances, damage developed already after 4-7 months. The next step was to inform the patient about his treatment options and the risk and benefit associated with reirradiation. Here, we might refer to Homer who described the dangerous travel between Scylla and Charybdis. Instead of accepting the rapid development of tumour-related spinal cord damage, the patient chose the slightly more attractive route, which offered hope for prolonged functional independence even if the ultimate outcome might not differ. Reirradiation was effective in stopping the rapid growth of the tumour, but did not result in partial remission. Eventually, the tumour damaged the spinal cord and irreversible deficits developed. Nevertheless, the reirradiation regimen of 30 Gy in 10 fractions appears reasonable with regard to risk-/benefit ratio. In spite of considerable retreatment experience in the authors' institution, the treatment decision was not easy. The cumulative biologically equivalent dose administered here was the third highest in the senior author's experience. The two other cases had received 205 Gy_2 (interval 6 months, survival after reirradiation 5 months, no myelopathy) [6] and 181.5 Gy_2 (interval 12 months, survival after reirradiation 8 months, no myelopathy) [5] in comparable situations where better sparing of the spinal cord was impossible. Based on our previous review [6], which included 11 patients with radiation myelopathy reported by Wong et al. [14], this late side effect might develop after 4-7 months (4 of 11 cases) or later during follow-up. Three out of eleven patients with myelopathy had received reirradiation with short interval (2-4 months), but the case reported here is among those with the shortest interval in the literature. The fact that some patients with high risk for radiation myelopathy might not develop this complication during their remaining life time should not encourage us to uncritically recommend reirradiation. However, under certain circumstances the decision appears justified and might result in clinical benefit. It is also important to notice that the high cumulative radiation dose was not given to the complete cross-section of the spinal cord. So far, there is very limited clinical data regarding the tolerance of the spinal cord to partial high-dose irradiation. Given the intriguing results of a recent randomised trial of bevacizumab versus placebo in patients with radiation necrosis of the brain [15], a condition which resembles pathophysiological characteristics of radiation myelopathy [16], it might be possible to envision a scenario where patients developing early signs of this complication can start with bevacizumab therapy, though it is currently unclear whether or not permanent protection from irreversible neurological deficits can be achieved.

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