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Carsten Nieder
Johannes Langendijk *Editors*

Re-Irradiation: New Frontiers

Second Edition

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Carsten Nieder • Johannes Langendijk
Editors

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Contents

Normal Tissue Tolerance to Reirradiation

Carsten Nieder and Johannes A. Langendijk

Contents

Abstract

As a result of longer survival times, even among patients with incurable malignancies, the prevalence of patients at risk of developing second primary tumours and/or locoregional recurrences in previously irradiated areas might increase. Consequently, the need for additional therapeutic measures providing local control and/or symptom palliation along different lines of treatment has emerged. This has resulted in increasing requests for delivering a second and sometimes even third course of radiation to target volumes within or close to previously irradiated anatomical areas. On the one hand, improved imaging and delivery techniques including image-guided and intensity-modulated radiotherapy might facilitate reirradiation of previously exposed regions of the body. On the other hand, late toxicity is of concern because it often causes serious impact on health-related quality of life. Therefore, knowledge about long-term recovery of occult radiation injury is of utmost importance. This chapter summarises available experimental and clinical data on the effects of reirradiation to various organs.

1 Introduction

The increasing number of publications on reirradiation demonstrates that many clinicians seriously consider this treatment modality in selected

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patients with favourable risk/benefit ratio. A large variety of regimens exists, which might be associated with quite different risks of toxicity, e.g. 2 fractions of 2 Gy for relapsed follicular lymphoma (Heinzelmann et al. 2010) as compared to repeat radiosurgery for intracranial targets (Raza et al. 2007; Holt et al. 2015) or brachytherapy for previously irradiated prostate cancer (Moman et al. 2009). Even radiation-induced tumours such as glioma might be considered for reirradiation (Paulino et al. 2008). Increasing the distance between organs at risk and the high-dose region, e.g. by injectable or implanted spacers, is an interesting approach (Kishi et al. 2009), but only feasible in certain anatomical sites and in a limited proportion of patients. Both experimental and clinical data have shown that a variety of normal tissues recover from occult radiation injury. However, decision-making on whether to reirradiate a patient is, indeed, a complex process. Factors to be taken into account include the type of tissue at risk for injury, the total dose, fractionation and interval from previous irradiation, observable normal tissue changes resulting from previous irradiation, the patient's prognosis, disease extent and so forth. The following paragraphs on experimental and clinical data on reirradiation tolerance of various tissues summarise our current knowledge and provide a basis for better understanding of the challenges associated with reirradiation to higher cumulative total doses.

2 Acute Reactions

2.1 Skin and Mucosa

In 1989, Terry et al. reported that the acute reactions of mouse foot skin receiving reirradiation 2 months or more after receiving a single dose of 15–30 Gy were indistinguishable from those of unirradiated skin. They also found that the tolerance to a second course of irradiation decreased and the latency to manifestation of acute reactions shortened when reirradiation was given 1 month after a previous course or when a single dose of 34.5–37.5 Gy was given, which was sufficient to produce a near-complete breakdown of the skin. Simmonds et al. (1989) reported comparable results for reirradiation of pig skin at intervals of 17, 35 or 52 weeks after single priming doses below the threshold for inducing moist desquamation. The regain in the acute tolerance of the skin to reirradiation is likely a result of the ability of the epidermis to respond to radiation-induced damage by accelerated repopulation and stem cell migration into the irradiated tissue leading to restoration of the original cell number and tissue integrity. Published clinical data on reirradiation of head and neck tumours, breast cancer, non-small cell lung cancer and others summarised in other chapters of this book also showed that acute skin and mucosal reactions after reirradiation were well within the range observed after the first course of radiotherapy (De Crevoisier et al. 1998; Montebello et al. 1993; Harms et al. 2004; Tada et al. 2005; Langendijk et al. 2006; Würschmidt et al. 2008; Tian et al. 2014). If the previous treatment has caused persistent severe mucosal damage, reirradiation might be poorly tolerated.

2.2 Intestine

There is only a single study on experimental reirradiation tolerance of the intestine (Reynaud and Travis 1984). Mice received 9 or 11.5 Gy whole abdominal irradiation, which did not cause acute mortality but reduced the jejunal crypt number by about 10% and caused 10% late mortality from intestinal damage within 1 year. Single graded doses of total body irradiation were then given after 2, 6 or 12 months. Assessment of crypt survival 3.5 days after reirradiation showed that very little, if any, of the initial abdominal radiation dose was remembered by the surviving crypts, indicating a remarkable tolerance to reirradiation. In the clinic, Haque et al. (2009) observed only one case of acute high-grade toxicity (grade 3 or higher) in 13 patients treated with reirradiation to the abdomen for gastrointestinal malignancies. These authors administered a hyperfractionated-accelerated regimen, using 1.5 Gy fractions twice daily, with a median dose of 30 Gy (range 24–48 Gy) and in most cases concurrent chemotherapy.

3 Late Side Effects

3.1 Epithelial and Mesenchymal Tissues

Simmonds et al. (1989) found in a pig model that there was no or little residual injury retained for late ischaemic dermal necrosis (corresponding to at most 2–7 % of the initial dose). Moreover, the latency for development of necrosis was not different. The exact mechanism underlying such recovery is not yet clearly understood. However, clinical data related to many cancer types revealed that late complications were more frequent than anticipated after reirradiation to high cumulative doses. For patients with mycosis fungoides ($n=14$) receiving a second course of total skin electron beam therapy (18–24 Gy after an initial dose of about 30 Gy), late skin toxicities included generalised xerosis, toenail and fingernail dystrophy and scattered telangiectasia (Ysebaert et al. 2004). The majority of data is derived from head and neck cancer retreatment. For example, the authors of a large series of 169 patients reirradiated for recurrent unresectable head and neck tumours after a median time of 33 months to a median cumulative dose of 130 Gy (some with concurrent chemotherapy) found 21 % and 8 % incidences of mucosal necrosis and osteoradionecrosis, respectively (De Crevoisier et al. 1998). Moderate late morbidity, such as trismus and cervical fibrosis, developed in up to 41 % of patients. Within their respective ranges, the reirradiation dose, cumulative dose, reirradiated volume or interval between the two treatment courses did not predict the risk of severe late injury. Other factors, such as perfusion disturbance after previous surgery or pre-existing cardiovascular diseases, might also impact on the eventual development of epithelial and connective tissue complications. Lee et al. (1997) reported the data of 654 patients with recurrent nasopharyngeal carcinoma receiving reirradiation to median initial and reirradiation doses of 60 Gy and 46 Gy, respectively, with a median interval of 2 years. The actuarial incidence of symptomatic late sequelae (for all complications combined) was approximately 50 % at 5 years. They found that the biologically effective dose (BED) of the first radiation course affected the risk of late injury significantly, the BED of reirradiation was of borderline significance, but the interval between both treatments was not significant. The potential effects of volume were not evaluated. In a later analysis, the same group found that the major determinant of post-retreatment complications was the severity of damage during the initial course (Lee et al. 2000). A study by Xiao et al. (2015) included 291 patients and found that gross tumour volume was predictive not only for the prognosis and risk of distant metastases, but also for toxicity-related death, e.g. resulting from massive haemorrhage. The prospective study by Tian et al. (2014) also showed that tumour volume significantly influenced the risk of mucosal necrosis (53 % if volume >26 cc vs. 23 % in smaller tumours). A small study of 16 patients who received amifostine together with postoperative reirradiation and chemotherapy for head and neck cancer did not suggest reduced late toxicity rates with this strategy (Machtay et al. 2004). Severe toxicity occurred also after intensity-modulated radiotherapy (IMRT) but no prospective head to head comparison of IMRT versus 3-D conformal RT is available (Sulman et al. 2009). In the IMRT study reported by Duprez et al. (2009), 84 patients were reirradiated to a median cumulative total dose of 130 Gy (median time interval 49.5 months, median reirradiation dose 69 Gy, 17 patients received concurrent chemotherapy). Late toxicity was scored in 52 patients with at least 6 months of follow-up. Eight patients developed grade 3 or 4 late dysphagia and three developed osteoradionecrosis. Overall, 30 different grade 3 or 4 late complications were recorded. Osteoradionecrosis might even develop in the cervical vertebrae, though the most common location is the mandible (Kosaka et al. 2010). Clearly, it is unrealistic to expect absence of any severe late toxicity after IMRT or other highly conformal techniques since certain parts of the mucosal and/or connective tissues will always be part of the planning target volume and receive high cumulative doses. This issue is further addressed in other chapters of this book. Overall, the available data indicate that the mesenchymal tissues recover from radiation

injury less than rapidly reacting tissues like the epidermis and mucosa, at least in the head and neck region.

3.2 Thoracic Aorta and Carotid Arteries

Reports of high-dose reirradiation have identified the large arteries as critical organs at risk. Evans et al. (2013) analysed the end point of grade 5 aortic toxicity in 35 patients with lung cancer. The median prescribed dose was 54 Gy in 1.8-Gy fractions and 60 Gy in 2-Gy fractions, respectively. The median interval between the two courses was 32 months. The median raw composite dose to 1 cc of the aorta was 110 Gy. Toxicity developed in 25% of patients who received ≥120 Gy but not in patients irradiated to lower cumulative doses. The issue of carotid blowout syndrome (CBOS) has been studied by Yamazaki et al. (2013). They pooled data from 7 Japanese CyberKnife institutions and analysed 381 patients. Of these 32 (8.4%) developed CBOS after a median of 5 months from reirradiation. Twenty-two patients died (69%). Later, a predictive model (CBOS index) was developed, which includes carotid invasion of >180°, presence of ulceration and lymph node area irradiation (0–3 points) (Yamazaki et al. 2015). A larger pooled series included 1554 patients who received head and neck reirradiation (McDonald et al. 2012). There were 41 reported CBOS, for a rate of 2.6, and 76% were fatal. The median time to CBOS was 7.5 months. In patients treated in a continuous course with 1.8–2 Gy daily fractions or 1.2 Gy twice-daily fractions, 36% of whom received concurrent chemotherapy, the rate of CBOS was 1.3%, compared with 4.5% in patients treated with 1.5 Gy twice daily in alternating weeks or with delayed accelerated hyperfractionation, all of whom received concurrent chemotherapy ($p=0.002$).

3.3 Intestine

Late toxicity data are available from a study of palliative reirradiation for recurrent rectal cancer (Lingareddy et al. 1997). In this study, 52 patients were reirradiated to approximately 30 Gy (once daily 1.8 or 2 Gy in 30 patients and bid 1.2 Gy daily in 22 patients) after an initial course of median 50.4 Gy. The median interval was 24 months. Twenty patients received an additional boost dose to a maximum of 40.8 Gy. Most patients ($n=47$) also had concurrent 5-fluorouracil chemotherapy with reirradiation. Grade 3 or 4 (by Radiation Therapy Oncology Group (RTOG) criteria) small bowel obstruction occurred in nine patients (17%), cystitis in three patients (6%) and non-tumour-related fistulas in four patients (8%). The cumulative dose, reirradiation dose and time interval were not significantly related to late toxicity. However, conventional fractionation with 1.8–2 Gy resulted in more toxicity as compared to hyperfractionation (hazard ratio 3.9). The latter finding was confirmed in a follow-up publication that included 103 patients (Mohiuddin et al. 2002). In this study, interval to reirradiation >24 months was also associated with significantly lower late toxicity rates. Fifteen percent of patients developed small bowel obstruction and 2% colo-anal stricture. Persistent severe diarrhoea was recorded in 17% of patients. As with many other studies discussed in this chapter, actuarial rates of late adverse events and detailed dose-volume histogram analyses were not provided. Another group performed reirradiation after omental flap transposition (OFT) in 12 patients with locoregional recurrent rectal cancers (Kim et al. 2010). No severe complications of grade 3 or higher involving the small bowel or bladder occurred. It was suggested that OFT effectively excluded small bowel from the radiation field. Intestinal complications also hampered the benefits of high-dose reirradiation of tumours in the female genital tract with combined external beam RT and brachytherapy (Russell et al. 1987). They were uncommon (one case of gastrointestinal bleeding classified as grade 4 late toxicity, no grade 3 adverse events among 13 patients) after palliative abdominal reirradiation to a median dose of 30 Gy given after an initial course of median 45 Gy (Haque et al. 2009). Abusaris et al. (2011, 2012) reported institutional dose constraints that also resulted in low rates of grade 3–4 toxicities, albeit in small groups of patients.

3.4 Lung

Terry et al. (1988) assessed the risk of pneumonitis after reirradiation in a mouse model. The whole thorax was irradiated with a priming dose of 6, 8 or 10 Gy, which did not cause changes in breathing rate or lethality. One to six months later, reirradiation was given (over a full range of doses). The end point of this experiment was radiation pneumonitis within 196 days after reirradiation. Both the size of the priming dose and the interval had a significant impact on the response to reirradiation. After a low priming dose of 6 Gy, the lungs could tolerate reirradiation as if they had not received previous radiation exposure. Some occult injury remained at 1 month after an 8-Gy priming dose. Residual damage in the order of 25–70 % persisted at all time intervals after a 10-Gy priming dose. The experimental set-up is different from the clinical situation where only limited parts of the lung receive irradiation. Moreover, the radiation dose to the heart might also impact on lung toxicity and late pulmonary function. Our own unpublished clinical experience with palliative reirradiation of lung cancer is consistent with published data, which suggest that pneumonitis is rarely observed (Montebello et al. 1993). For example, Jackson and Ball (1987) observed no symptomatic radiation pneumonitis among 22 patients with non-small cell lung cancer reirradiated to 20–30 Gy in 2-Gy fractions after having received a median dose of 55 Gy (median interval 15 months). A Japanese study with 15 patients (median reirradiation dose 50 Gy in 25 fractions, median interval 16 months) reported one case of grade 3 radiation pneumonitis and three cases of grade 2 esophagitis (Tada et al. 2005). After brachytherapy, severe toxicity was uncommon too (Hauswald et al. 2010). Apparently, the lungs recover at least partially from occult injury. Experimental data on trachea, bronchi or oesophagus are lacking. Most clinical series did not describe particular problems with these critical structures, except for stereotactic treatment of central lesions. Also after proton beam reirradiation, oesophageal fistula (raw dose 136 Gy) and tracheal necrosis (raw dose 147 Gy) have been reported (McAvoy et al. 2013). Of note, however, is that the median survival after moderate-dose reirradiation was only 5–7 months and, hence, was too short for assessment of true late damage to the lungs and other thoracic structures. As shown in Fig. 1, lung fibrosis might develop in patients with longer survival. Experience with higher reirradiation doses is still limited and typically derived from small-field stereotactic radiotherapy series (Peulen et al. 2011; Liu et al. 2012; Meijneke et al. 2013).

3.5 Spinal Cord

Reirradiation tolerance of the spinal cord has been most extensively studied in animal models using paresis, predominantly resulting from white matter necrosis that manifests in 10–12 months in rodents, as the end point and the median paresis dose (ED_{50}) for computation. Results of two reirradiation experiments revealed that the fractionation sensitivity of reirradiation was similar to that of single-course irradiation (Ruifrok et al. 1992a; Wong et al. 1993). Lower spine reirradiation experiments (T10-L2 in adult mice, L3–5 in adult rats, L2–6 in young guinea pigs) showed remarkable long-term recovery if the initial dose was limited to 50–75 % of the ED_{50} (Hornsey et al. 1982; Lavey et al. 1994; Knowles 1983; Mason et al. 1993). The extent of injury retained was highest after initial irradiation to 75 % of the ED_{50}, but even under this condition, only 30 % of injury was retained. A series of reirradiation experiments of rat cervical spinal cord showed that the initial dose, the interval to reirradiation and the reirradiation dose influenced the latency to myelopathy (Wong et al. 1993; Wong and Han 1997). Beyond an 8-week interval, there was a progressive increase in recovery with an increasing time interval to reirradiation, but recovery was never complete. In adult rats main long-term recovery occurred between 2 and 6 months. For 3-week-old rats, partial recovery took place during the first month, which increased only slightly between 1 and 6 months (Ruifrok et al. 1992b). In a different study, an initial single dose of 15 Gy was administered, followed 8 or

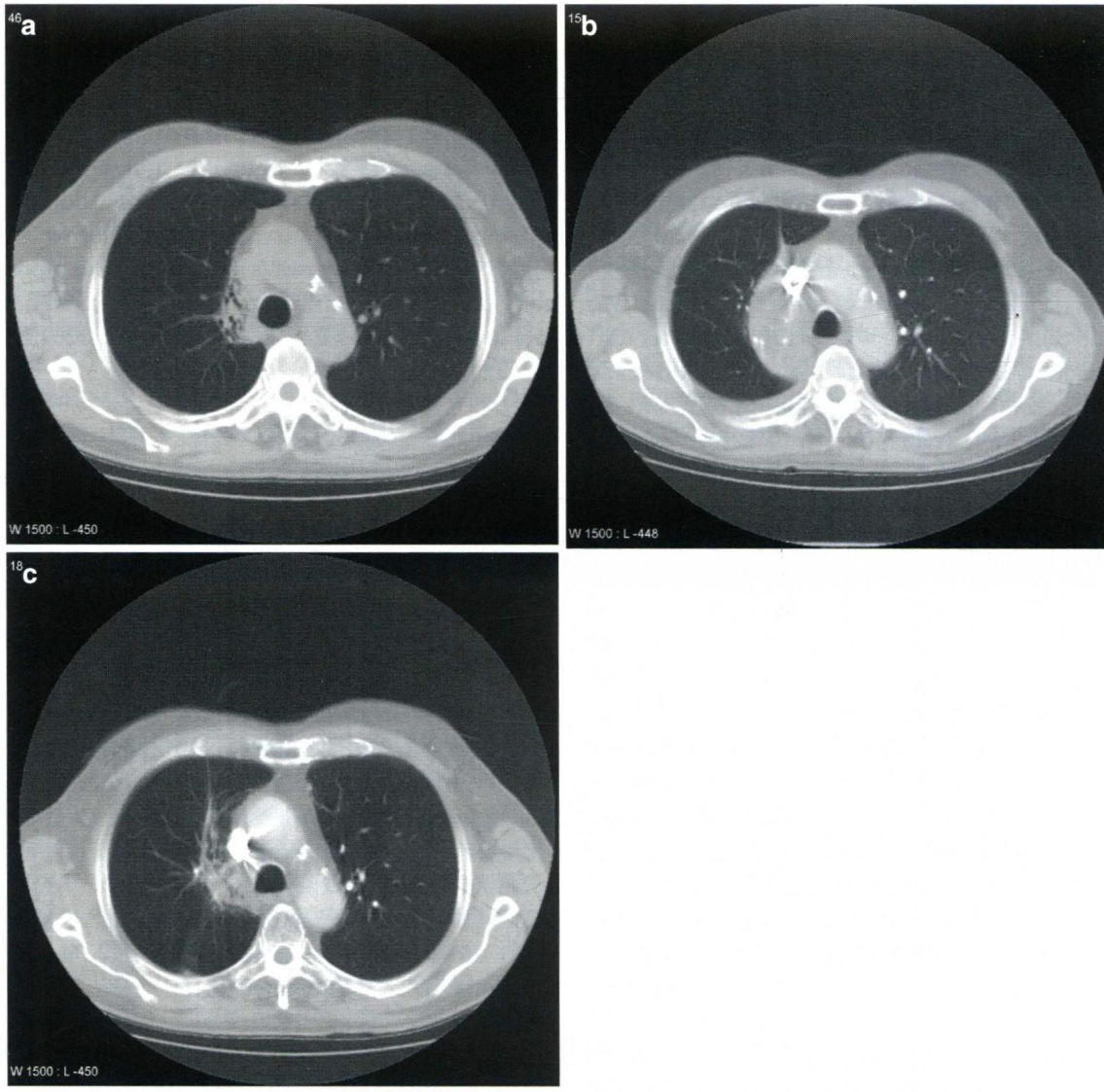

Fig. 1 In 1995, a 58-year-old gentleman received combined chemoradiation for small cell lung cancer of the right lung (limited disease) resulting in a cure. (**a**) Shows a follow-up computed tomography (CT) scan from 2008 demonstrating slight paramediastinal radiation fibrosis. In January 2009, the patient was diagnosed with stage IIIB adenocarcinoma of the right lung (**b**). He received two cycles of platinum-based chemotherapy and achieved a partial response. He went on to simultaneous chemotherapy and 3D-conformal reirradiation (15 fractions of 2.8 Gy). He developed grade III acute esophagitis but no pulmonary toxicity. (**c**) Shows the most recent CT scan taken 1 year after reirradiation demonstrating increasing radiation fibrosis in the reirradiated region (clinically asymptomatic). At that time the patient was diagnosed with multiple brain metastases and started palliative whole-brain irradiation (no previous prophylactic whole-brain radiotherapy had been given)

16 weeks later by additional graded doses (van der Kogel 1979). In contrast to all other studies, separate dose-response curves were obtained for white matter necrosis (latent period <7 months) and vascular damage (latent period up to 18 months). Recovery between 8 and 16 weeks was significant for the white matter necrosis end point but was much less for vascular damage. It has also been shown that modification of the reirradiation tolerance of the spinal cord can be obtained (Nieder et al. 2005a). In these experiments, a combination of systemically administered insulin-like growth factor-1 and intrathecal amifostine resulted in lower incidence of myelop-

athy after cervical spinal cord reirradiation in rats. Such strategies were not pursued further because of increasing availability of equipment and software, which allows for spinal cord sparing (IMRT, stereotactic RT etc.). Other pharmacologic strategies aiming at radioprotection in different tissues and organs typically were examined in previously untreated animals (Greenberger 2009) although the reirradiation setting appears attractive for studying radioprotectors.

As compared to rodent experiments, more clinically applicable data were generated in adult rhesus monkeys at MD Anderson Cancer Center, Houston, USA, by Ang et al. (1995). The cervical spinal cord of these primates was irradiated with 2.2 Gy per fraction. The control group received a single radiation course to total doses of 70.4, 77 or 83.6 Gy. The number of animals developing myelopathy in these 3 dose groups was 3 of 15, 3 of 6 and 7 of 8, respectively. Twelve asymptomatic animals in the 70.4 Gy group were retreated 2 years later to cumulative doses of 83.6, 92.4 or 101.2 Gy (four animals each). Only two developed paresis at 11 (83.6 Gy) and 8 (92.4 Gy) months after reirradiation. Subsequently, 16 monkeys received 44 Gy in 20 fractions and 2 years later were reirradiated to cumulative doses of 83.6, 92.4, 101.2 or 110 Gy. Only two (one received 101.2 Gy and the other 110 Gy) developed myelopathy. These data indicate that a substantial amount of the occult injury induced by the priming dose decayed within 2 years. As published in 2001, Ang et al. confirmed their initial observations in a group of 56 rhesus monkeys. The dose of the initial course was 44 Gy in all monkeys. Reirradiation dose was 57.2 Gy, given after 1-year ($n=16$) or 2-year ($n=20$) intervals, or 66 Gy, given after 2-year ($n=4$) or 3-year ($n=14$) intervals. Only 4 of 45 monkeys completing the required observation period (2–2.5 years after reirradiation, 3–5.5 years total) developed myelopathy. Fitting the data with a model, assuming that all (single course and reirradiation) dose-response curves were parallel, yielded recovery estimates of 33.6 Gy (76%), 37.6 Gy (85%) and 44.6 Gy (101%) of the initial dose, after 1, 2 and 3 years, respectively, at the 5% incidence level. Another way to look at these results is to estimate the total cumulative dose that can be tolerated, expressed in EQD_2 that is equivalent dose in 2-Gy fractions calculated using the linear-quadratic approach. For a time interval of 1, 2 and 3 years between the treatment courses, cumulative doses of 150, 156 and 167% of the first-line setting's tolerance dose appear possible.

If true in humans, an initial exposure equivalent to 46 Gy in 2-Gy fractions (arbitrarily selected to represent 100% of the tolerance dose at the 5% myelopathy risk level because many institutions limit the spinal cord dose to lower levels than true tolerance (Kirkpatrick et al. 2010)) might be followed by an additional 23–24 Gy in 2-Gy fractions (50% of the tolerance dose) 1 or 2 years later. Clinical data from different institutions supporting this interpretation have been published (Schiff et al. 1995; Grosu et al. 2002). Most patients were treated with palliative reirradiation and therefore follow-up was often limited. In patients with better prognosis, the cumulative spinal cord dose often was kept at very low levels, e.g. in the RTOG head and neck cancer reirradiation protocols (Langer et al. 2007). Nevertheless, data from patients with longer follow-up have been published, e.g. five patients with recurrent Hodgkin's disease who were followed for more than 5 years after reirradiation (Magrini et al. 1990). The first spinal cord dose was 30 Gy in 1.7 Gy fractions (plus chemotherapy) and 1–3 years later up to 40 Gy in 2-Gy fractions was administered (two to three vertebral segments) without causing myelopathy. The cumulative EQD_2 of this treatment is slightly lower than 150%. All available data from different published series including those reporting on myelopathy (Wong et al. 1994) were analysed by Nieder et al. (2005b, 2006a). Seventy-eight patients were included and a risk prediction model was developed, based on time interval, cumulative dose and presence or absence of any treatment course resulting in quite high spinal cord exposure. Besides cumulative dose, interval <6 months and total dose equivalent to >50 Gy in 2-Gy fractions in one of the two courses increases the risk of myelopathy. Low-risk patients had <5% risk of myelopathy and intermediate risk patients approximately 25%. However,