Fractionation Concepts

Carsten Nieder and Michael Baumann

Contents

Abstract

This chapter summarizes the principles of fractionated radiotherapy and altered fractionation approaches. Clinical reirradiation examples and isoeffect calculations are provided. The vast majority of published reirradiation series consist of retrospective data or small prospective studies with limited statistical power. In addition, the typical patient populations are more heterogeneous than in first-line radiotherapy studies. For example, patients with local relapse, regional relapse, or second primary tumors might be included. Therefore, the level of evidence is not comparable to that of first-line radiotherapy, where many treatment recommendations and guidelines are based on large and well-designed prospective randomized trials or meta-analyses of several trials. Reirradiation is often used for palliative symptoms but occasionally curative approaches, which require high total radiation doses, might be possible. Hyperfractionated reirradiation might theoretically improve the therapeutic ratio, but prospective trials are required to confirm this hypothesis.

1 Background

Radiobiological research during the twentieth century has indicated that fractionation of the total radiation dose often produces better tumor control for a given level of normal tissue toxicity than a single large dose. Better normal tissue sparing might result from repair of sublethal damage between dose fractions.

C. Nieder (✉)
Department of Oncology and Palliative Medicine, Nordland Hospital, Prinsensgate 164, 8092 Bodø, Norway
e-mail: carsten.nieder@nlsh.no

M. Baumann
Department of Radiation Oncology, University Hospital Carl Gustav Carus, Fetscherstr. 74, 01307 Dresden, Germany

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Beneficial effects such as reoxygenation of tumor cells and reassortment of cells into radiosensitive phases of the cell cycle may contribute to better tumor control for the same level of normal tissue damage when compared to single dose application. However, more recently it was also realized that prolonged overall treatment time might result in repopulation of cancer cells and thus be disadvantageous. In many clinical instances, regimens consisting of administration of 1.8–2 Gy once daily five times per week were considered standard (Hellman 1975; Greenberg et al. 1976; Holsti et al. 1978; Beck-Bornholdt et al. 1997). Clinical interest in the use of more and smaller dose fractions in radical radiotherapy has been stimulated by experimental normal tissue studies (Stewart et al. 1984). It has been found that if the dose per fraction is reduced (i.e., in hyperfractionation where a higher number of fractions of less than 1.8 Gy is given, usually two fractions per day), then there is sparing of late-responding normal tissues relative to those which respond early (Withers et al. 1982; Withers 1985; Niewald et al. 1998). This phenomenon can be understood in terms of the shapes of the underlying dose effect relationships, which can be described using the linear quadratic equation. The ratio (alpha/beta) of the linear (alpha) and quadratic (beta) terms is a useful measure of the curviness of such dose effect curves. Low alpha/beta values (1.5–5 Gy) have been observed for late-responding normal tissues and indicate that radiation damage should be greatly spared by the use of dose fractions smaller than the 1.8–2 Gy used in conventional radiotherapy. By contrast, the high alpha/beta values (6–14 Gy) observed for acutely responding normal tissues indicate that the response is relatively linear over the dose range of clinical interest. Hence, less extra sparing effect is to be expected if lower doses per fraction are administered. If tumors respond in the same way as acutely responding normal tissues, then hyperfractionation might confer a therapeutic gain relative to late-responding normal tissues. Basically, this effect is caused by differences in repair capability. Clinical studies of hyperfractionation assumed that moderate escalation of the total dose would improve tumor control rates without causing excess late complications (Fig. 1). However, the radiation fractions should not be given too close together, certainly not closer than 6 h, because of incomplete damage repair (Joiner 1993, Baumann and Gregoire 2009).

In the context of reirradiation, the issue of normal tissue toxicity is of utmost importance. While acute toxicity largely is comparable to that of first-line treatment, late toxicity resulting from high cumulative radiation doses might often be observed (Simmonds et al. 1989; Stewart 1999). Chronically progressive fibrosis, stenosis, and perfusion deficits resulting in tissue necrosis have been described. Their impact on quality of life and organ function might be severe. With regard to palliative reirradiation, late toxicity might not become clinically apparent during the limited life span of most patients. However, the situation might be different in patients treated with curative intent (Nieder et al. 2000). It is therefore necessary to assess the biologically effective dose (BED) and late effects of the initial course of radiotherapy and to exclude patients who tolerated their previous treatment poorly. In addition, efforts must be made to limit the volume of reirradiated normal tissues. Today's improved target volume imaging and definition approaches as well as image-guided high precision techniques contribute to volume reduction and improved dose distribution. Harnessing such technology might even allow for hypofractionated short-course reirradiation as demonstrated, e.g., in palliative treatment of head and neck cancer (Heron et al. 2010), recurrent high-grade gliomas (Grosu et al. 2005; Nieder et al. 2008; Fogh et al. 2010), and stereotactic radiosurgery of vestibular schwannomas (Yomo et al. 2009) or spinal metastases (Choi et al. 2010). Single doses were also given with intraoperative approaches, e.g., in rectal cancer (Haddock et al. 2001). In addition, several brachytherapy regimens have been used, e.g., in prostate and head and neck cancer (Burri et al. 2010). Hypofractionation, intraoperative radiotherapy, and radiosurgery do not form the focus of this chapter. The disease-specific chapters provide details on such approaches. In a recent Canadian survey on reirradiation, many respondents recommended brachytherapy or highly conformal external irradiation techniques (Joseph et al. 2008). Hyperfractionated schedules were suggested as a means of limiting retreatment toxicity. Obviously, hyperfractionation was among the few strategies available in the past and also utilized by one of the authors of this chapter in the 1990s (Nieder et al. 1999) before positron emission tomography (PET), intensity-modulated radiotherapy (IMRT), tomotherapy and other tools became a part of our armamentarium.

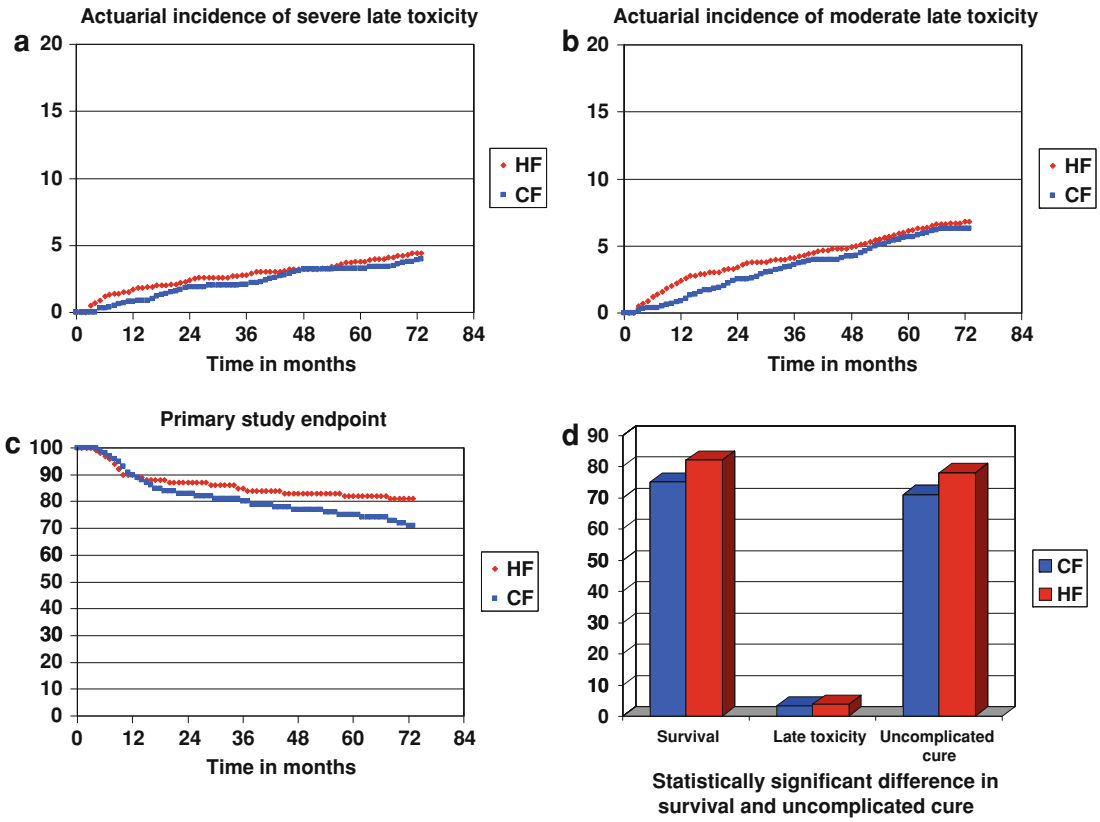

Fig. 1 **a–d** Hypothetical outcome of hyperfractionated (HF) as compared to conventional radiotherapy (CF), e.g., in head and neck squamous cell carcinoma. Actuarial curves displaying the primary study endpoint, e.g., overall survival and development of late toxicity. Hyperfractionated radiotherapy results in a therapeutic gain and increased rate of uncomplicated cure, i.e., survival without serious side effects

Reirradiation is not a new idea, some clinical studies were published already more than 30 years ago and some of these included patients treated as early as 1940 (Shehata et al. 1974; Fu et al. 1975; Hunter and Stewart 1977; Laramore et al. 1978; Dritschilo et al. 1981). The same holds true for accompanying experimental studies (Brown and Probert 1975). The vast majority of published reirradiation series consist of retrospective data or small prospective studies. In addition, the typical patient populations are more heterogeneous than in first-line radiotherapy studies. For example, patients with local relapse, regional relapse or second primary tumors might be included. Therefore, the level of evidence is not comparable to that of first-line radiotherapy, where many treatment recommendations and guidelines are based on large and well designed prospective randomized trials or meta-analyses of several trials. However, it appears that reirradiation not only palliates cancer-related symptoms but under certain circumstances might contribute to improved survival, especially in diseases where local control determines survival (Jereczek-Fossa et al. 2008). One example is the recent study of 108 children with relapsed ependymoma where 66% received radiotherapy at relapse and 50% of older children were reirradiated and where reirradiation was associated with better outcome (Messahel et al. 2009). In a smaller study, which included 25 patients with previously irradiated recurrent medulloblastoma, a trend towards better event-free survival was seen in patients who received additional radiotherapy as part of their retrieval therapy (Dunkel et al. 2010). Limited evidence is also available from reirradiation of benign tumors such as pituitary adenoma (Schoenthaler et al. 1992).

2 Hyperfractionation in First-Line Radiotherapy

The clinical evaluation of hyperfractionated radiotherapy in patients with advanced squamous cell carcinoma of the head and neck started in the 1970s (Meoz et al. 1984). EORTC protocol 22791 compared once daily fractionation of 70 Gy in 35–40 fractions in 7–8 weeks, to pure hyperfractionation of 80.5 Gy in 70 fractions in 7 weeks using two fractions of 1.15 Gy per day (i.e., same conventional overall treatment time), in T2–T3 oropharyngeal carcinoma (excluding base of tongue), node negative or N1 of less than 3 cm (Horiot et al. 1992). From 1980 to 1987, 356 patients were randomized. As published in 1992, the local control was significantly higher ($P = 0.02$) after hyperfractionation. The multivariate Cox model confirmed that the treatment regimen was an independent significant prognostic factor for locoregional control ($P = 0.007$). This improvement of locoregional control was responsible for a trend to an improved survival ($P = 0.08$). There was no difference in late normal tissue damage between the two treatment modalities, although some controversy exists about the certainty to which differences in normal tissue damage may be excluded by this and other trials (Baumann et al. 1998; Baumann and Beck-Bornholdt 1999; Bentzen et al. 1999; Fallai and olmi 1997). Several trials of unconventional fractionated radiotherapy in head and neck squamous cell carcinoma followed, e.g., by the RTOG (Fu et al. 2000) but the effect of such treatment on survival remained unclear. A meta-analysis of updated individual patient was performed (Bourhis et al. 2006). Trials were grouped in three pre-specified categories: hyperfractionated, accelerated, and accelerated with total dose reduction. Tumor sites were mostly oropharynx and larynx; 74% of patients had stage III–IV disease. There was a significant survival benefit with altered fractionated radiotherapy, corresponding to an absolute benefit of 3.4% at 5 years (hazard ratio 0.92, 95% CI 0.86–0.97; $P = 0.003$). The benefit was significantly higher with hyperfractionated radiotherapy (8% at 5 years) than with accelerated radiotherapy (2% with accelerated fractionation without total dose reduction and 1.7% with total dose reduction at 5 years, $P = 0.02$). There was a benefit on locoregional control in favor of altered fractionation versus conventional radiotherapy (6.4% at 5 years; $P < 0.0001$), which was particularly efficient in reducing local failure, whereas the benefit on nodal control was less pronounced.

Certain side effects such as development of radiation retinopathy might also be less likely in patients with head and neck cancer treated with hyperfractionated radiotherapy. In a study by Monroe et al. (2005), 186 patients received a significant dose to the retina as part of curative radiotherapy. Primary sites included nasopharynx, paranasal sinus, nasal cavity, and palate. Hyperfractionated radiation was delivered to 42% of the patients in the study, typically at 1.1–1.2 Gy per fraction. The remainder were treated once daily. Thirty-one eyes in 30 patients developed radiation retinopathy, resulting in monocular blindness in 25, bilateral blindness in 1, and decreased visual acuity in 4. The actuarial incidence of developing radiation retinopathy was 20% at both 5 and 10 years. Higher retinal doses resulted in a steady increase in the incidence of retinopathy, with 25 of the 30 cases occurring after 60 Gy or more. Of the patients receiving more than 50 Gy to the retina, hyperfractionation was associated with a significantly lower incidence of radiation retinopathy (37% vs. 13%; $P = 0.0037$). On multivariate analysis, retinal dose ($P < 0.0001$) and fractionation schedule ($P = 0.0003$) were significant predictors of radiation retinopathy.

Patients with localized unresectable non-small cell carcinoma of the lung were also treated with hyperfractionated regimens, e.g., 1.2 Gy twice daily (Seydel et al. 1985). Of the 120 eligible patients, 10 received a dose of 50.4 Gy, 20 received 60.0 Gy, 79 received 69.6 Gy, and 11 patients received 74.4 Gy. Complete regression occurred in 19% of T1–T3, N0–N2 patients. There were six cases of severe and two of life-threatening toxicity, but there were no fatalities attributable to the treatment. Toxicity consisted mainly of pneumonitis and pulmonary fibrosis as well as esophagitis. Median survival of the entire group was 7.2 months, which was consistent with previous experience at that time. It was later found that all five of the 5-year survivors came from the 79 patients assigned to receive 69.6 Gy (Cox et al. 1991). Combined stages II and III 5-year survival rates were 8% for 69.6 Gy compared to 6% for standard once-a-day irradiation in concurrent RTOG trials. A randomized phase III trial shed more light on the issue of hyperfractionation (Sause et al. 1995). Three arms

were evaluated: (1) standard radiation therapy, (2) induction chemotherapy followed by standard radiation therapy, and (3) twice-daily radiation therapy. Patients were required to have a Karnofsky performance status of 70 or more and weight loss less than 5% for 3 months before entry into the trial. Of the 490 patients registered in the trial, 452 were eligible. The disease in 95% of the patients was stage IIIA or IIIB. Patients were randomly assigned to receive either 60 Gy of radiation therapy delivered at 2 Gy per fraction, 5 days a week, over a 6-week period (standard radiation therapy), induction chemotherapy consisting of cisplatin and vinblastine followed by standard radiation therapy starting on day 50, or 69.6 Gy delivered at 1.2 Gy per fraction twice daily. One-year survival (%) and median survival (months) were, respectively, as follows: standard radiation therapy—46%, 11.4 months; chemotherapy plus radiotherapy—60%, 13.8 months; and hyperfractionated radiation therapy—51%, 12.3 months. The chemotherapy plus radiotherapy arm was statistically superior to the other two treatment arms ($P = 0.03$). This was confirmed in a later analysis of the trial (Sause et al. 2000). Other groups explored hyperfractionation in non-randomized studies of early-stage non-small cell lung cancer (Jeremić and Milicić 2008; Jeremic et al. 1997). However, other developments (continuous hyperfractionated accelerated radiotherapy, concomitant chemoradiation, stereotactic body radiotherapy, etc.) outperformed classical hyperfractionation, which has not evolved into a standard of care in non-small cell lung cancer.

Hyperfractionated radiotherapy was studied in a large variety of other cancer types, but no general benefit was found. One of the unsuccessful examples is high-grade gliomas (Nieder et al. 2004). None of the glioma studies reviewed in 2004 reported a significant improvement in survival by altered fractionation in comparison to either institutional historical controls or their respective randomized control arm.

3 Hyperfractionated Reirradiation

In contrast to first-line radiotherapy where systematic efforts were undertaken to compare different fractionation regimens, no such randomized comparisons are available. The retrospective series reported by Bauman et al. (1996) included 17 patients with primary CNS tumors, who received hyperfractionated reirradiation and 17 patients treated with once-daily fractionation (Table 1). Some children, e.g., with medulloblastoma were included in this heterogeneous population. Median overall survival was 8.3 months in all 34 patients. The actuarial risk of necrosis was 22% at 1 year after retreatment. Fractionation had no statistically significant influence on overall survival, progression-free survival, or increased complications in this study with limited statistical power. A retrospective comparison in patients with rectal cancer was reported in 1997 (Lingareddy et al. 1997). The study included 52 patients, 22 of whom opted for hyperfractionated radiotherapy while the others preferred conventional once-daily treatment, mainly for logistical reasons. Ninety percent received concomitant 5-FU. Fractionation had no statistically significant influence on overall survival, but late toxicity was significantly reduced in patients who had received hyperfractionated treatment (relative risk 3.9, 95% confidence limit 1.1–14.4). No such correlation was found in the retrospective study of reirradiation for rectal cancer patients who underwent resection after reirradiation with concurrent 5-FU (Mohiuddin et al. 1997). Another study in rectal cancer where all patients received hyperfractionated reirradiation reported relatively moderate rates of late toxicity (necessitating surgery in only one patient, Table 1), but 15% serious postoperative complications in those patients who eventually underwent tumor resection after chemoradiation (Valentini et al. 2006). The other two studies summarized in Table 1 were not designed to evaluate the impact of hyperfractionation on outcome. Thus, there is very limited evidence supporting the hypothesis that hyperfractionated reirradiation, which is challenging with regard to logistics and resource utilization, would improve the therapeutic index by reducing late toxicity. On the other hand, the regimens evaluated so far were administered with more or less outdated treatment planning approaches and technology, resulting in unnecessary large volumes of irradiated normal tissues. This might lead to the conclusion that a randomized trial of conventional versus hyperfractionated reirradiation utilizing, e.g., IMRT would be of interest.

Table 2 summarizes the results of hyperfractionated accelerated reirradiation. In these studies, the typical dose per fraction was 1.5 Gy. If one intends to administer a total dose of 45 Gy in a

Table 1 Hyperfractionated reirradiation: study overview

Reference	Study type	Disease site	Number of patients	Interval between series	Reirradiation	Side effects	Median survival
Lingareddy et al. (1997)	Retrospective	Locally recurrent rectal cancer	22 out of 52 in the study	Minimum 3 months, median 24 months[a]	30 Gy with or without additional boost, varying total doses, 1.2 Gy b.i.d., typically with concurrent 5-FU	Acute grade III toxicity in 31%[a]. Late grade III–IV toxicity in 33%[a]	12 months[a]
Mohiuddin et al. (1997)	Retrospective	Locally recurrent rectal cancer	21 out of 39 in the study	Minimum 3 months, median 18 months[a]	30 Gy with or without additional boost, varying total doses, 1.2 Gy b.i.d., typically with concurrent 5-FU, resection 8–12 weeks later	Treatment break or termination in 18%[a]. Delayed wound healing in 7%[a]. Severe late toxicity in 28%[a]	45 months[a]
Valentini et al. (2006)	Multicenter phase II	Locally recurrent rectal cancer	59	Minimum 9 months, median 27 months	30 Gy + 10.8 Gy boost, 1.2 Gy b.i.d., concurrent 5-FU, resection 6–8 weeks later, then chemotherapy	12% of patients developed late toxicity	42 months
Popovtzer et al. (2009)	Retrospective	Recurrent squamous cell head and neck cancer	31 out of 66 in the study	Minimum 6 months, median 37 months[a]	Total dose 70 Gy at 1.25 Gy b.i.d. with concurrent cisplatin and 5-FU	Acute grade III–V in 10%. Late grade III–V in 29%	Approximately 19 months (estimated from the published graph)[a]
Benchalal et al. (1995)	Pilot study	Head and neck cancer	19	Minimum 9 months, median 30 months	Total dose 60 Gy at 1.2 Gy b.i.d.	Acute grade III toxicity in 47%. Late grade III toxicity in 11%	Approximately 18 months (estimated from the published graph)
Bauman et al. (1996)	Retrospective	Primary central nervous system tumors	17	Minimum 3.7 months, median 17.5 months	Total dose 30–44 Gy, in some cases over 60 Gy at 1.0 Gy b.i.d.	1 case of necrosis, 1 of cognitive decline, 1 of increased tumor cyst	Not reported

[a] Relates to all patients including those treated with conventional fractionation

Table 2 Hyperfractionated-accelerated reirradiation: study overview (not all head and neck cancer studies are shown)

Reference	Study type	Disease site	Number of patients	Interval between series	Reirradiation	Side effects	Median survival (months)
Abdel-Wahab et al. (1997)	Pilot study	Relapsed brain metastases	15	Minimum 8 weeks, median 10 months	Limited brain fields after previous WBRT; 1.5 Gy b.i.d., median 30 Gy	No serious toxicity	3.2
Nieder et al. (1999)	Retrospective	Relapsed high-grade gliomas	32	Minimum 8 weeks, median 20 months	Limited brain fields; 1.3 Gy b.i.d., total dose 45.5 Gy (during the later part of the study 1.5 Gy b.i.d., total dose 45 Gy)	16% late toxicity including 2 patients with radionecrosis	8.5
Spencer et al. (2008)	Multi-institutional prospective trial RTOG 9610	Unresectable recurrent squamous cell carcinoma of the head and neck	79	Minimum 0.6 years, median 2.5 years	4 Weekly cycles of chemoradiotherapy separated by 1 week of rest; 1.5 Gy b.i.d., total dose 60 Gy	6 deaths in acute period, acute grade IV in 18%, late grade III and IV in 22%, feeding tube at last follow-up in 70%	8.5
Watkins et al. (2009)	Retrospective	Locoregionally recurrent head and neck tumors	39	Minimum 0.5 years, median 2.3 years	4 Weekly cycles of chemoradiotherapy separated by 1 week of rest; 1.5 Gy b.i.d., total dose 60 Gy	4 deaths in acute period, acute grade IV in 10%, late grade III–V in 56%	19
Haque et al. (2009)	Retrospective	Gastrointestinal tumors (pancreas, bile duct, colon etc.)	13	Minimum 5 months, median 26 months	Typically 30–39 Gy total dose, 1.5 Gy b.i.d.	Late grade III toxicity: 0, late grade IV toxicity: 1 (8%)	14
Das et al. (2010)	Retrospective	Rectal cancer	50	Minimum 0.4 years, median 2.3 years	If interval < 1 year: 30 Gy If interval ≥ 1 year: 39 Gy 1.5 Gy b.i.d. Typically with concurrent capecitabine	Late grade III or IV toxicity: 13 (26%)	26

WBRT whole brain radiotherapy, *RTOG* Radiation Therapy Oncology Group

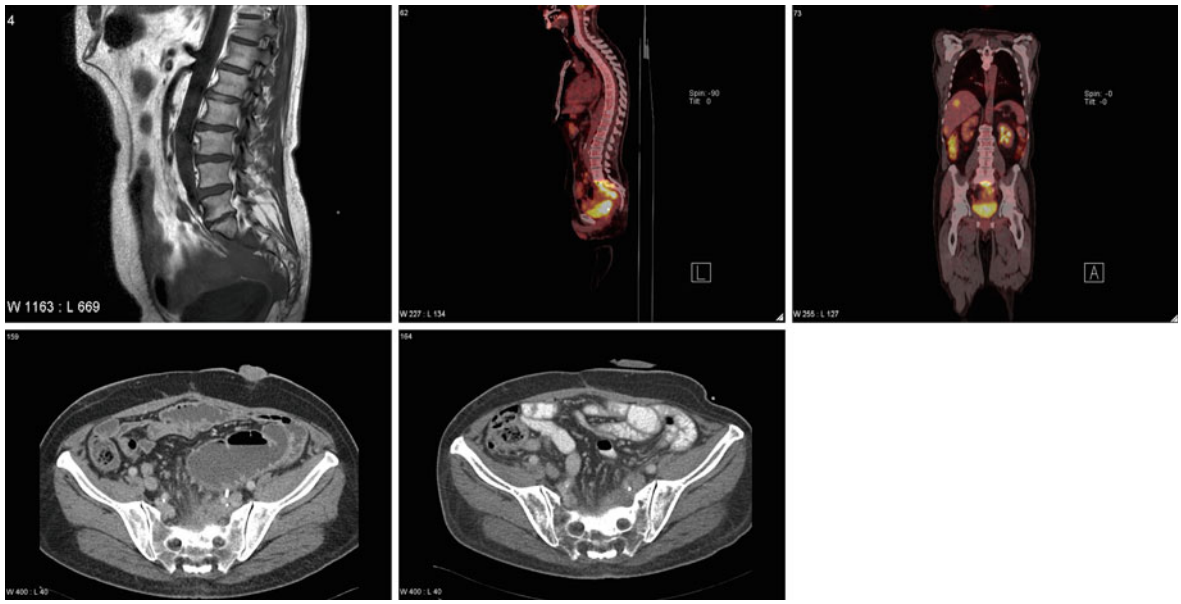

Fig. 2 An illustrative case from one of the authors' institutions (Nordland Hospital, Bodø, Norway). A 56-year-old man was diagnosed with anal cancer stage T3 N0 M0 in 1997. He received radiotherapy (40 Gy plus 10 Gy boost in 2-Gy fractions) with concomitant 5-FU and mitomycin-C. In 2001, the patient developed local relapse and was salvaged surgically. In 2007, both local relapse in the presacral region and liver metastases were detected. Palliative chemotherapy was initiated, first cisplatin and 5-FU, then 5-FU and mitomycin-C. Because of increasing pelvic pain, the patient was referred for palliative reirradiation in December 2008. The liver metastases were stable. No obvious late toxicity from the initial course of radiotherapy was present. The patient's Karnofsky performance status (KPS) at that time was 70. We considered the following key questions: (i) Is the patient's performance status at a level that justifies initiation of radiation therapy? Yes, the KPS was 70. (ii) Do laboratory tests point to advanced hepatic disease and/or poor tolerability/efficacy of the planned therapy? No, the only abnormal finding was slight anemia and elevated alkaline phosphatase. (iii) Are other disease sites absent or controlled and if so, does one expect continued disease control? The liver metastases were stable. (iv) Will systemic treatment be offered or are there no more options left? Taxane-based chemotherapy was an option. (v) Will local control impact on the survival of the patient or is treatment focused on palliation of symptoms? The aim was palliation of pelvic pain. (vi) Might the cumulative radiation dose to critical normal tissue structures result in serious toxicity in patients with expect prolonged survival? The probability of bowel or bladder toxicity, insufficiency fracture, or nerve damage was considered low and the same holds true for the probability of long-term survival. (vii) How did the tumor respond to initial radiotherapy, and how long is the interval? Complete remission was obtained in 1997, and the interval of 11 years did permit reirradiation. The magnetic resonance, positron emission tomography (PET), and computed tomography (CT) images above show the presacral tumor mass, its bony extension, two liver metastases, and a ureter stent. Tables 1 and 2 provide an overview on rectal cancer reirradiation studies, which might guide in decision making. When deciding between hyperfractionated, conventional, and hypofractionated three-dimensional conformal radiotherapy in this case, the following facts were considered. The planning target volume resulting from the PET–CT-defined gross tumor volume did not include large volumes of bowel or bladder. The interval from initial treatment was very long. No concomitant chemotherapy would be added because the patient previously had heavy exposure to the standard drugs. Because of a lack of clinical data in the reirradiation setting, taxanes or oxaliplatin were not considered. Thus, we decided that hypofractionated reirradiation appeared feasible in this palliative setting. The patient received 12 fractions of 3 Gy in January 2009. He developed urinary infection and received antibiotics and a new stent. No other acute complications or toxicity were registered. Pelvic pain improved, though not completely. No additional systemic treatment was given. At the last follow-up in February 2010, the presacral tumor was stable (CT image on the right hand side), and the patient was without obvious late toxicity

hyperfractionated accelerated fashion, i.e., 1.5 Gy b.i.d., 15 treatment days are needed. This compares to 25 treatment days when once-daily treatment with 1.8 Gy per fraction is chosen. As with hyperfractionated reirradition, no randomized trials have been published. Given the design and size of the available studies, no definitive conclusions can be drawn. However, comparison with studies where

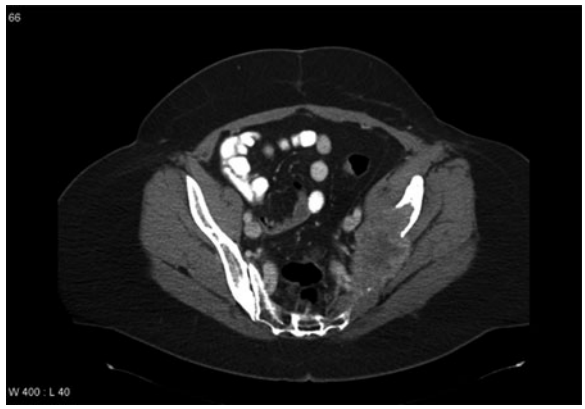

Fig. 3 An illustrative case from one of the authors' institutions (Nordland Hospital, Bodø, Norway). A 49-year-old woman was diagnosed with metastasized high-grade leiomyosarcoma of the uterus with multiple lung metastases and two bone metastases in 2005. After hysterectomy, she received three cycles of adriamycin without objective response. Palliative radiotherapy to a large painful pelvic bone metastasis (computed tomography (CT) image above) was given in May 2006; the total dose was 39 Gy in 13 fractions of 3 Gy. Two anterior–posterior opposing fields were used. The lesion diminished in size (<50% reduction) and then remained stable until February 2008 when the patient presented with increasing pain and bone destruction and was referred for reirradiation. She had not received second-line chemotherapy. With regard to potential side effects and fractionation of reirradiation, the following considerations are important. On a planning CT scan with empty bladder, the amount of reirradiated bladder was judged to be minimal. Bony structures had to be reirradiated to full dose as they were part of the clinical target volume. The same holds true for certain muscles and soft tissue. The skin could be spared to a large degree with three-dimensional treatment planning. The major organs at risk were small and large bowel, and the sacral and presacral nerve roots, and nerves. When calculating the BED of the first irradiation course, one has to keep in mind that two opposing fields were used resulting in a maximum dose to parts of the bowel of 105% of the prescribed dose, which was 3 Gy. Thus, these parts had received 13 fractions of 3.15 Gy. We will use an alpha/beta value of 3 Gy in this example. The resulting BED is $13 \times 3.15 \times (1 + 3.15 \div 3)$, i.e., 84 Gy_3, according to the formula $n \times d \times (1 + d \div$ alpha/beta value) where n is the number of fractions, and d the dose per fraction. This dose is actually equivalent to 50 Gy in 25 fractions of 2 Gy (BED 83 Gy_3). If one wishes to limit the reirradiation BED to the equivalent of 40 Gy in 20 fractions of 2 Gy (BED 67 Gy_3), then the following alternatives result: 40 Gy in 20 fractions of 2 Gy, 35 Gy in 14 fractions of 2.5 Gy (BED 64 Gy_3), 30 Gy in 10 fractions of 3 Gy (BED 60 Gy_3), 28 Gy in 7 fractions of 4 Gy (BED 65 Gy_3) and, of course, lower doses such as 20 Gy in 5 fractions of 4 Gy. For an alpha/beta value of 4 Gy, the same reirradiation schedules would be feasible. The previous regimen of 39 Gy in 13 fractions had resulted in a quite long palliative benefit, and no obvious late toxicity. The choice will now depend on the patient's life expectation and willingness to accept the possible consequences of bowel, soft tissue, and nerve toxicity. Other factors such as travel distance might also impact on the patient's preference.

conventional fractionation was employed in the same cancer types does not provide strong indications for improved efficacy or therapeutic ratio. This should be considered in clinical decision making, as illustrated in the example provided in Fig. 2. Figure 3 elaborates on the usefulness of isoeffect calculations in reirradiation scenarios. The BED obtained with different fractionation regimens is calculated, and shown in Tables 3 and 4.

4 Low-Dose Ultrafractionation

Given a recent publication on this unconventional reirradiation approach, the principles including a historical perspective will be reviewed briefly. In an early clinical trial, 168 patients with carcinoma of the bladder, T2–T4, were randomized to one of two treatments, 1.0 Gy 3 times a day to a total dose of 84 or 2 Gy once a day to a total dose of 64 Gy (Edsmyr et al. 1985). Both treatments were given over 8 weeks with a rest interval of 2 weeks in the middle of the treatment period. This is different from current chemoradiation approaches in bladder cancer. Local eradication of the tumor in the bladder cystoscopically and cytologically at 6 months after completion of treatment and patient survival were analyzed. The results favored significantly the patients treated with 84 Gy. A report from 1994 included all patients after a follow-up period of at least 10 years (Näslund et al. 1994). The survival benefit from dose-escalated hyperfractionation initially reported after 5 years was

Table 3 Isoeffect calculations: the biologically effective dose (BED) of different fractionation regimens is shown (formula $n \times d \times (1 + d \div$ alpha/beta ratio) where n is the number of fractions, and d the dose per fraction as described in Baumann and Gregoire 2009)

	Tumor cells and acute responding normal tissues alpha/beta ratio 10 Gy	Spinal cord alpha/beta ratio 2 Gy	Other late-responding normal tissue alpha/beta ratio 3 Gy	Other late-responding normal tissue alpha/beta ratio 4 Gy
First course, 60 Gy in 30 fractions of 2 Gy, once daily	72 Gy_{10}	Exceeds commonly accepted constraints	100 Gy_3	90 Gy_4
Same fractionation, but normal tissue sparing[a]		79 Gy_2[a] Equivalent to 40 Gy in 2-Gy fractions	67.5 Gy_3[a] Equivalent to 40 Gy in 2-Gy fractions	62 Gy_4[a] Equivalent to 42 Gy in 2-Gy fractions

It is assumed that acute responding tissues react to reirradiation in the same manner as to first-line radiotherapy. Regarding late-responding tissues, it has been demonstrated that the fractionation sensitivity of the rat cervical spinal cord during reirradiation was not significantly different from the fractionation sensitivity of not previously irradiated control rats, with an alpha/beta ratio of 2.3 Gy in control rats and 1.9 Gy during reirradiation of the spinal cord (Ruifrok et al. 1992). The alpha/beta ratio of tumors might vary. A second primary squamous cell carcinoma in the aerodigestive tract might have the same alpha/beta ratio as a squamous cell carcinoma treated several years earlier in the same patient. However, that might not necessarily be true for a locally recurrent squamous cell carcinoma arising from malignant cells that survived a radical course of radiotherapy and where the surviving clonogens might be biologically different from the ones that could be eradicated

[a] The maximum normal tissue dose in this example is 30 fractions of 1.5 Gy, i.e., 75% of the prescription dose of 2 Gy

still evident after 10 years. The effect was detectable in all the three stages (T2, T3, and T4) and in the pooled data. However, it only reached statistical significance in the T3 subset, and in the total pooled data set. An improvement in local control was seen but the differences were not statistically significant. Complications in the bowel requiring surgical treatment were more common in the hyperfractionated group but with the statistical power (number of events) of this trial the difference was not significant. During the same era, comparable fractionation regimens were studied in breast cancer patients, but they never entered clinical routine (Notter and Turesson 1984). It was then shown in tumor cell lines, many of them considered radioresistant, that excessive low-dose hyper-radiosensitivity at fraction doses ≤ 0.5 Gy might exist, and several radiobiological explanations for this phenomenon were discussed (Joiner et al. 2001; Short et al. 2001; Tomé and Howard 2007; Simonsson et al. 2008). However, studies on tumor models in vivo, including those generated from cell lines showing low dose hyper-radiosensitivity in vitro, failed to show any advantage of ultrafractionated radiotherapy with three doses of 0.4 Gy per day of 6 weeks compared to conventional fractionation to the same dose (Krause et al. 2003, 2005a, b).

The reirradiation study included 11 highly selected adult patients (Pulkkanen et al. 2007). Three-dimensional conformal beam radiotherapy was used. Three fractions of 0.5 Gy (nine patients) or 0.6–0.66 Gy were given daily 4 h apart. The total dose was 30–51 Gy (median 45 Gy) with treatment times of 28–46 days. The minimum interval was 1 year, median 6 years. Previous radiotherapy typically had been given with 50–60 Gy. Favourable local control was observed in patients with grade II and III gliomas. Three patients with rectal cancer progressed locally after 3–12 months. One patient with lung metastasis from rectal cancer progressed locally after 10 months. However, palliation of symptoms could be achieved. Neither acute nor late toxicity was observed. In this small series, it is difficult to estimate with regard to efficacy the impact of favorable tumor biology as indicated by the long time interval from initial radiotherapy to relapse. The time interval might also explain the toxicity results. It is thus not clear whether comparable outcome might have been obtained with other fractionation regimens, which demand less resources and are more convenient to patients.

Table 4 The hypothetical patient from Table 3 is considered for different reirradiation scenarios where the spinal cord is the major dose-limiting organ

Dose to tumor	Dose to spinal cord	Spinal cord BED alpha/beta ratio 2 Gy	Comment on cumulative spinal cord BED[a], interval >6 months	Comment on cumulative spinal cord BED[a], shorter interval
First course, 60 Gy in 30 fractions of 2 Gy, once daily	30 Fractions of 1.5 Gy	79 Gy_2 Equivalent to 40 Gy in 2-Gy fractions		
Reirradiation 8 Gy in 1 fraction	1 Fraction of 8 Gy	40 Gy_2 Equivalent to 20 Gy in 2-Gy fractions	119 Gy_2 Equivalent to 60 Gy in 2-Gy fractions Myelopathy risk score 0	119 Gy_2 Equivalent to 60 Gy in 2-Gy fractions Myelopathy risk score 4.5
Reirradiation 30 Gy in 10 fractions of 3 Gy, once daily	10 Fractions of 3 Gy	75 Gy_2 Equivalent to 38 Gy in 2-Gy fractions	154 Gy_2 Equivalent to 76 Gy in 2-Gy fractions Myelopathy risk score 4	154 Gy_2 Equivalent to 76 Gy in 2-Gy fractions Myelopathy risk score 8.5
Reirradiation 30 Gy in 15 fractions of 2 Gy, once daily	15 Fractions of 2 Gy	60 Gy_2 Equivalent to 30 Gy in 2-Gy fractions	139 Gy_2 Equivalent to 70 Gy in 2-Gy fractions Myelopathy risk score 2	139 Gy_2 Equivalent to 70 Gy in 2-Gy fractions Myelopathy risk score 6.5
Reirradiation 60 Gy in 30 fractions of 2 Gy, once daily	30 Fractions of 1.4 Gy	71 Gy_2 Equivalent to 36 Gy in 2-Gy fractions	150 Gy_2 Equivalent to 74 Gy in 2-Gy fractions Myelopathy risk score 3	150 Gy_2 Equivalent to 74 Gy in 2-Gy fractions Myelopathy risk score 7.5
Reirradiation 60 Gy in 30 fractions of 2 Gy, once daily	30 Fractions of 1.0 Gy	45 Gy_2 Equivalent to 22 Gy in 2-Gy fractions	124 Gy_2 Equivalent to 62 Gy in 2-Gy fractions Myelopathy risk score 1	124 Gy_2 Equivalent to 62 Gy in 2-Gy fractions Myelopathy risk score 5.5

[a] Myelopathy risk derived from Nieder et al. (2006) (based on cumulative BED, interval between the two radiotherapy courses <6 months and BED of one course ≥102 Gy_2, i.e., the equivalent of more than 50 Gy in 2-Gy fractions)

A risk score of ≤3 points suggests a myelopathy risk of <5%, i.e., comparable to that of previously unirradiated patients

A risk score of 4–6 points suggests a myelopathy risk of approximately 25%

A risk score of >6 points suggests a myelopathy risk of approximately 90%

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