Strahlenschutzkommission

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Management of unplanned treatment interruptions in medical radiation therapy

Recommendation by the German
Commission on Radiological Protection

Adopted at the 297th meeting of the German Commission on Radiological Protection on 13. and 14. December 2018

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Ausfallkonzepte in der Medizinischen Strahlentherapie

Empfehlung der Strahlenschutzkommission

Preface

In radiation therapy, the total dose is generally broken down into individual fractions, which are administered over a time period defined in a radiotherapy treatment plan. This approach allows doctors to exploit the different radiobiological repair capacities of tumour cells and healthy body cells so that normal tissue in the irradiated volume is spared. If the planned overall treatment time is extended due to interruptions, for example due to equipment failure, this can have an adverse effect on the treatment objective.

Accordingly, the licensing procedures for the operation of installations for generating ionising radiation and of irradiation facilities for medical applications of radiation require the applicant to describe the measures taken to ensure that, in the event of a technical failure of these irradiation facilities, patients can receive ongoing treatment within the scope of the radiobiological requirements in order to achieve the intended treatment objective.

With a view to enshrining appropriate guidelines for contingency planning in secondary legislation, the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU) asked the Commission on Radiological Protection (SSK) for a recommendation on more-detailed requirements for contingency planning on the basis of current scientific findings.

In order to draft this recommendation, a working group entitled "Management of unplanned treatment interruptions in medical radiation therapy" was set up as part of the SSK's Committee on Radiological Protection in Medicine. The working group had the following members:

- Prof. Dr. Cordula Petersen (Hamburg)
- Prof. Dr. Mechthild Krause (Dresden)
- PD Dr. med. Dipl.Phys. Karim-Maximilian Niyazi (München)
- Dipl.-Ing. Volker Steil (Mannheim)
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- Prof. Dr. Klemens Zink (Gießen)

The working group was assisted by Professor Nestle, Chair of the Committee on Radiological Protection in Medicine from 2015 to 2016.

This recommendation proposes measures to compensate for non-prescribed breaks in radiotherapy treatment due to technical and/or organisational reasons. It also highlights that the urgency of compensation for treatment breaks depends on the type of tumour and the clinical indication for radiotherapy, and that contingency planning must therefore account for different priority levels among the affected patients.

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Content

1 Introduction

Radiation therapy is an important therapeutic modality for the treatment of cancer.

The targeted use of ionising radiation destroys tumour cells in a defined target volume. The therapeutic objective may be the complete elimination of tumours (curative treatment) or the alleviation of tumour-related complaints (palliative treatment). Radiotherapy can be used after an operation as a form of adjuvant therapy or, in the absence of an operation, to treat a tumour that is still present in the body (definitive radiation therapy). It can be performed alone or in combination with drugs that act on the tumour (e. g. combined radiochemotherapy). Even some benign diseases (e. g. benign tumours of the nervous system) can be treated analogously using radiation therapy.

Therapeutic irradiation is rarely delivered on a one-off basis (so-called radiosurgery); rather, it is generally fractionated. This means that the planned total dose is divided into individual fractions, which are administered over a period ranging from several days to several weeks. The reason for this fractionation is that tumour cells and healthy body cells have different radiobiological repair capacities, with fractionation generally resulting in the sparing of normal tissue within the irradiated volume. The size of the prescribed single and total dose is specified by the specialist physician and is determined based on the underlying disease and therapeutic objective. In individual cases, it may also be necessary to adjust the prescribed total and single dose during treatment based on medical requirements or new findings. Extensive specialist literature deals with the investigation of the optimum dose and fractionation of radiation therapy for a wide range of oncological and non-oncological diseases. Based on the administered single dose and the prescribed timing, a distinction is usually made between normofractionated therapies, which typically involve a single dose of 1.8 Gy to 2 Gy, hyperfractionated/ accelerated regimes, in which more than five fractions are administered per week with the same dose per fraction, and hypofractionated concepts with single doses > 2 Gy per fraction.

Generally speaking, therefore, key factors include not only the total dose and the size of the irradiated volume but also the fractionation and hence the duration of treatment.

As a rule, the standards on dose and fractionation assume consistent treatment in which radiation is administered every working day from the start to the end of the course of radiotherapy (i. e. for the prescribed overall treatment time). If there are interruptions in treatment, the overall treatment time is therefore extended. For patients, this can have an adverse impact on the therapeutic objective.

As clonogenic tumour cells proliferate (repopulate) during a treatment break, the clinical results of radiotherapy may be impaired. Indeed, there is experimental and clinical data (see section 2) showing that, as the overall treatment time increases, a greater radiation dose is needed for tumour control. Likewise, it can be concluded from retrospective analyses that uncompensated treatment breaks lead to a worsening of clinical outcomes. In radiation oncology, this has led to the concept of a “time factor”, which implies a reduction in tumour control probability with increasing overall treatment time for fractionated radiation therapy with an identical therapeutic dose.

The causes for unplanned treatment interruptions may lie with the patient, for example if individual doses are not administered or are delayed due to intercurrent diseases or complications or due to reasons of patient compliance. The management of these interruptions requires medical decisions to be taken on a case-by-case basis. In contrast, this recommendation deals with technical and/or organisational causes of treatment interruptions and their management. Possible reasons generally include planned maintenance as well as equipment failures. Germany has a diverse radiotherapy landscape, ranging from major university hospitals with

multiple pieces of technically diverse equipment to smaller hospital departments or practices with individual solutions. The changing framework conditions on the market, as well as high procurement costs and rapid technical development, mean that even larger facilities often operate a range of technically diverse apparatus. The aim of this recommendation is to help ensure that, in this complex system, patients receive care in accordance with the Radiation Protection Ordinance (StrlSchV).

Given the aforementioned importance of treatment interruptions, radiotherapy facilities in Germany are required to present a contingency plan so that, in the event of equipment failure or scheduled unavailability (e. g. maintenance), radiotherapy treatment can be continued using another device (BMU 2011, Euratom 2014). The absence of clear instructions for this until now led the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU) to ask the German Commission on Radiological Protection (SSK) for a recommendation on aspects to be considered in contingency planning. These were to be based on current scientific findings and take account of new and increasingly established types of therapy using particle beams – especially proton and heavy-ion therapy.

This recommendation, M*anagement of unplanned treatment interruptions in medical radiation therapy*, proposes measures to compensate for non-prescribed breaks in radiotherapy treatment due to technical and/or organisational reasons.

2 Background

The strongest evidence for the existence of a time factor relates to carcinomas of the head and neck area and the lungs (Hansen et al. 1997, Bese et al. 2007). For example, when patients were treated with radiotherapy alone in randomised trials of head and neck tumours, a reduction in the overall treatment time by one week (with worse acute side effects, as expected) led to an approximately 12% improvement in local tumour control (Overgaard et al. 2003). Comparable increases have also been published in relation to bronchial carcinomas (Saunders et al. 1997). Retrospective studies or post hoc analyses of prospective studies also suggest a time factor for other tumour entities, including cervical and prostate cancer (Perez et al. 1995, Petereit et al. 1995, Thames et al. 2010). In the case of prostate cancer, a pooled analysis of approx. 4,500 patients revealed a 6% decrease in biochemical control after five years when the overall treatment time was extended by one week. This observation was confined to low- and intermediate-risk carcinomas treated with more than 70 Gy. For breast cancer too, retrospective data and especially a post hoc cumulative analysis of the START-A/B randomised trials of hypofractionated radiotherapy (Haviland et al. 2016) show that prolongation of overall treatment time leads to worse outcomes. Here, the "wasted dose" was equal to 0.6 Gy for each day by which the overall treatment time was extended relative to the original treatment plan. This data suggests that, even in the case of hypofractionated breast radiotherapy, it is vital to compensate for treatment breaks.

Firstly, contingency planning in medical radiotherapy should consider technical factors relating to radiation administration that ensure the precision and reproducibility of ongoing radiotherapy treatment. Secondly, any radiobiological needs that define the overall oncological situation (type of primary tumour and curative/palliative therapeutic objective) should also be considered and met.

3 Classification of patients in the event of equipment failure

As a minimum requirement, it is important to avoid deviating from the overall treatment time, as set out in the radiotherapy treatment plan, by more than one week other than for medical reasons (StrlSchV 2018).

Furthermore, in the event of device failure, it is sensible for the specialist doctor to classify the affected patients into urgency groups with regard to the measures needed to compensate for the break. These groups are based on the indication (curative/palliative) and evidence relating to the time factor. The examples below serve as a guide.

Group 1: Curative treatment approach for tumour entities where a significant time factor is demonstrated. Continuation of treatment is assessed as very urgent.

For example, these include head and neck tumours, lung cancer, cervical cancer, oesophageal cancer, cancer of the rectum, vulval/vaginal carcinomas and, by analogy, squamous cell carcinomas in other localisations. For these types of tumour, the adverse effect of extending the overall treatment time on the prognosis is well documented in the literature.

Every missed fraction should be compensated for. In the case of simultaneous radiochemotherapy, it should also be ensured that the chemotherapy is administered on radiotherapy treatment days.

Group 2: Curative treatment approach for tumour entities where a time factor is demonstrated but is less pronounced than in Group 1. Continuation of treatment is assessed as urgent.

These include all tumours subject to curative treatment that do not fall within Group 1, such as breast cancer, prostate cancer, glioblastomas, atypical or fast-growing meningiomas, and sarcomas. With respect to the patient, the curative treatment approach means that an analogous effect to Group 1 is to be assumed here, although the literature does not provide proof of this on the same scale in all cases. Here too, every missed fraction should be compensated for if possible.

Group 3: Benign tumours receiving treatment with a curative objective (e. g. low-grade meningiomas, vestibular schwannomas) and palliative therapy or therapy for inflammatory/degenerative diseases.

It is not strictly necessary to compensate for the break, providing it is ensured that the overall treatment time is not extended by more than one week. The need to compensate for a break, e. g. when urgently indicated based on the symptoms, is determined by the specialist physician.

*Table 3.1: General guidance for classification of patients with regard to urgency of compensation for treatment interruptions**

Group	Time factor	Examples	Therapeutic objective	Type of treatment	Compensation for every fraction	OTT**
1	Reliable	Head and neck tumours, lung cancer, cervical cancer, oesophageal cancer, cancer of the rectum, vulval/vaginal carcinomas	Curative	Radiotherapy alone, radiochemotherapy	Strongly recommended, chemotherapy only on radiotherapy treatment days	It is not permitted to exceed the OTT by more than one week.
2	To be assumed	Prostate cancer, glioblastomas, sarcomas	Curative	Sole or combined therapy	Recommended	It is not permitted to exceed the OTT by more than one week.
3	Not proven	Benign tumours, palliative treatment	Curative or palliative	Generally radiotherapy only	Not necessary	It is not permitted to exceed the OTT by more than one week.

* This classification is not to be equated with the classification into indication groups according to the SSK statement *Festlegung von Reaktionsschwellen und Toleranzgrenzen für die Prüfung des Gesamtsystems bei der perkutanen Strahlentherapie mit Photonen und Elektronen* ("Specification of reaction thresholds and tolerance limits for testing the entire system during percutaneous radiotherapy with photons and electrons"; SSK 2018) in order to define technical tolerance ranges

** OTT: overall treatment time

4 Measures to compensate for treatment breaks

Based on the fractionation, the overall treatment time is specified by the specialist physician. In cases of prolonged unavailability of equipment, whether scheduled (e. g. maintenance) or unscheduled (e. g. equipment failure), the equipment capacity may not be sufficient to treat all patients for the overall treatment time without interruption. In this case, the urgency set out above for individual patient groups should be regarded as definitive (Groups 1 to 3). The following forms of compensation for treatment breaks are prudent from a radiobiological perspective:

In the case of **normofractionated therapy** (1.8 Gy to 2 Gy/fraction, five times a week), the treatment break should be compensated for by administration of an additional fraction per week within the same treatment series (in total, a maximum of six fractions per week to avoid increased acute toxicity): irradiation either as a second daily fraction with a gap of at least six hours from the previous irradiation (ideally eight hours for tumours close to critical structures for delayed toxicity) or administration over a weekend.

Alternatively, treatment breaks can be compensated for by moderate hypofractionation or by increasing the total dose through additional fractions at the end of the course of radiotherapy. However, this requires the normal tissue planning constraints to be corrected based on the biologically effective dose calculated using the linear-quadratic (LQ) model.

In the case of the **hyperfractionated/accelerated therapy concept** (more than five fractions per week at the same dose per fraction), compensation should be achieved with additional treatment days at weekends, as otherwise the daily dose would be too high.

In the case of **hypofractionated radiotherapy concepts** (>4 Gy/fraction), compensation should preferably be achieved through additional treatment days at weekends, or a prolongation of the overall treatment time should be accepted if necessary; however, when **moderately hypofractionated treatment schemes** (>2 Gy to 4 Gy/fraction) are used, the aforementioned possibilities can be weighed up against the administration of a second fraction on one treatment day. In that case, however, an interval of at least eight hours should be observed from the preceding and subsequent fractions and, when multiple fractions are to be compensated for, care should be taken to spread the fractions across the therapeutic cycle. An extension of the overall treatment time should only be accepted up to the aforementioned limit (i. e. no more than one week).

In principle, **radiotherapy involving particles** is subject to the same rules as apply to that involving photons. If the break is so long that compensation no longer seems possible according to the above criteria, then the compensation concept should be to switch over to photon-beam radiotherapy. In principle, it would also be conceivable to transfer patients to other particle therapy centres. However, given the complexity of the therapy and the limited availability of treatment places, this hardly seems practical.

Clinically relevant example calculations for compensating for treatment breaks based on the linear-quadratic model can be found in the textbook *Basic Clinical Radiobiology* (Joiner and van der Kogel 2009).

5 Organisational and technical implementation of contingency plans

Radiotherapy facilities in Germany must maintain a technical contingency plan so that, in the event of equipment failure, treatment can be continued using another device (BMU 2011, Euratom 2014). Various scenarios exist for this:

a. The facility operates two identical or at least technically compatible irradiation devices (tandem concept). These would therefore be technically coordinated in such a way that plans no longer need to change when patients are switched over from one irradiation device to the other. This is the ideal scenario, as it ensures frictionless compensation for treatment breaks.

b. The facility operates multiple non-identical irradiation devices. In this case, organisational measures should be taken to ensure that, in the event of a failure, the physical parameters of the existing treatment plan can be adapted to the operational device to the extent that treatment can be continued promptly and to the same standard. For high-risk patients, it is necessary to check on a case-by-case basis whether a second radiotherapy treatment plan must be drawn up in order to avoid treatment breaks.

c. The facility only operates one irradiation device. Here it is necessary to resort to other radiotherapy departments, even if these are located at large distances from the original site. In this scenario, a cooperation agreement must set out in writing how and in what time frame the failure will be compensated for. Especially those facilities delivering radiotherapy in inpatient conditions must present a credible transport concept with reasonable transport times and logistics, as well as the necessary additional irradiation capacities at the cooperation partner's facility.

The following remarks apply to the cooperation arrangements that must be entered into:

- If the cooperation agreement includes further treatment by another specialist doctor, a consultation between the specialists should be arranged and documented in order to ensure continuity of treatment.
- The technical cooperation process should be arranged so as to ensure continued treatment within the planned overall treatment time while adhering to the biological and medical recommendations set out in this concept (analogously to a or b).
- If a radiotherapy treatment plan cannot be transferred from one device to the other, it should be ensured that a plan of the same standard can be drawn up promptly at the other facility based on the initial planning parameters.
- It should be ensured that additional plans are drawn up to deliver the entire treatment regime at the cooperating centres.
- It should be possible to implement the contingency plan within the next two working days, and the concept should take account of the irradiation capacities of the cooperation partner(s).

6 Recommendation

The SSK recommends:

- avoiding prolongation of the overall treatment time by more than a week for reasons not related to the patient.
- also minimising shorter interruptions to radiation therapy. For this purpose, the radiotherapy facility should maintain a written radiobiological concept.
- classification of affected patients into urgency categories (e. g. analogous to those in Table 1) by the specialist physician based on treatment indication and therapeutic objective according to Table 1, and compensation for treatment breaks in accordance with the assigned urgency category.
- that the radiotherapy facility also maintain a written concept setting out the technical compensation measures in the event of equipment failures. The aim is to achieve tandem solutions, ideally with identical irradiation devices. The devices used in tandem must be physically coordinated in such a way that plans no longer need to change when patients are switched over from one irradiation device to the other. Within the scope of the operating licence, concepts that deviate from these stipulations must be supported by, for example, a cooperation agreement in accordance with section 5.
- ensuring that the quality of the cumulative dose distribution is maintained within the medical and physical tolerance limits in the event of a change in irradiation technique (SSK 2018).

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