Strahlenschutzkommission

Geschäftsstelle der
Strahlenschutzkommission
Postfach 12 06 29
D-53048 Bonn

http://www.ssk.de

Patient follow-up as part of quality assurance in radiation therapy to monitor the outcome of treatment

Recommendation by the German
Commission on Radiological Protection

Adopted at the 251st meeting of the German Commission on Radiological Protection on 25th October 2011

The German original of this English translation was published in 2011 by the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety under the title:

Nachsorge als Teil der Qualitätssicherung in der Strahlentherapie zur Überprüfung des Behandlungserfolges

Empfehlung der Strahlenschutzkommission

This translation is for informational purposes only, and is not a substitute for the official recommendation. The original version of the recommendation, published on www.ssk.de, is the only definitive and official version.

Contents

Recommendation

Patient follow-up carried out subsequent to radiation therapy in order to monitor the outcome of treatment is an essential component of both individual treatment and quality assurance used with applied therapy methods. The results of the follow-up data will provide insights that help us to optimise the process and therefore play a part in justifying the process pursuant to the German Radiation Protection Ordinance (StrlSchV). As a result, the Guidelines for Radiation Protection in Medicine (RL StrlSch Med) stipulate that follow-up is the responsibility of the physician with relevant radiation protection expertise who administers the therapy (hereinafter referred to as radiotherapist, also commonly known as radiation oncologist or nuclear medicine specialist). The radiotherapist can transfer the patient to a suitable physician who is permitted to carry out certain aftercare measures. The physician is in turn required to submit the results to the radiotherapist.

It is only possible to ensure that the effects of treatment along with the early and, above all, late and extremely late side effects of radiation exposure and subsequent tumours are correctly documented if every patient is monitored long enough to allow any potential side effects to occur. The follow-up process is to be considered as part of the treatment, and the time period set aside for this is independent of the document retention periods set out in the German Radiation Protection Ordinance. The document retention period must be extended if there are findings that can be linked to the applied treatment.

The requirement for systematic documentation of side effects is the drafting of standardised records containing the data and parameters required to perform patient follow-up quality assurance. To this end, care must be taken to ensure that documentation can be transferred between systems as this is currently not the case. There is therefore a need to conduct research into data transferability between various documentation systems and in order to optimise records.

When collecting data during patient follow-up as part of the radiation therapy quality assurance process to monitor the outcome of treatment, care must be taken to ensure that privacy guidelines are complied with. Quality assurance and optimisation in terms of the safety of future patients are a top priority and any current impediments need to be removed. The general and clinical cancer registers also need to be included in the documentation and evaluation concept, which in turn requires pertinent legal guidelines.

The structural, staffing and financial requirements for proper follow-up also need to be clarified and documented, and this also includes appropriate cost reimbursements and funding of suitable research plans during the design phase.

The development and introduction of effective patient follow-up as part of the radiation therapy quality assurance to monitor the outcome of treatment requires a structured concept that can be developed in stages. In order to achieve this, the SSK recommends the following:

1. Follow-up provided as a quality assurance measure for radiation therapy patients must remain the responsibility of the physician with relevant radiation protection expertise who administers the therapy.
2. The follow-up period of radiation therapy and nuclear medicine therapy must be in line with the anticipated disease progression and latency periods of the potential side effects.
3. The scientific associations for radiotherapists are to draft reports on the type and scope of data to be collected for individual tumour entities and update them with the latest scientific findings.

4. When it comes to performing follow-up of radiation therapy, sustainable structures need to be created and existing ones optimised.
5. This means that stable structures need to be put in place to collect, store and evaluate data, and funding for suitable research plans may also be required.

The most pressing matter at hand is the need for a legal basis so that these recommendations can be implemented.

Scientific reasoning

1 Introduction

Teletherapy, brachytherapy or nuclear medicine therapy can be used to expose patients to ionising radiation for medical purposes. With teletherapy (percutaneous radiation therapy), the radiation source is outside of the body, whereas with brachytherapy, the radiation source is placed next to or inside the area requiring therapy. Nuclear medicine therapy involves the application of open radioactive substances.

For the remainder of this document, the physician with relevant radiation protection expertise who administers the ionising radiation therapy shall be known as the radiotherapist. This includes in particular radiooncologists and nuclear medicine specialists.

Indications of the need for radiation therapy include malignant and benign tumours. One factor common to each type of therapy is the fact that a significant volume of normal tissue is also always subject to high dose of radiation and thus represents a risk of side effects (unwanted effects of radiation).

Over the last few decades there have been major technical and physical advancements in especially in radiooncology in terms of therapy planning and application. This in turn has led to a change in spatial dose distribution within the patient that is also frequently linked to an expansion of the low-dose volume. An extreme example of this involves the application of just a few very high single doses within the scope of intracranial and extracranial stereotactic radiation therapy. Improved therapy protocols mean much higher tumour control rates and prolonged patient life expectancies. On the other hand, the use of highly conformal dose distributions, the improvement of target volume concepts and the use of steeper gradients at the target volume limit are all potential causes of recurrances and place high demands on the quality of treatment planning and execution. In nuclear medicine, therapeutic radiopharmaceuticals have continued to be developed which in turn has helped to expand the range of indications. In addition, radiation therapy is increasingly being combined with antineoplastic chemotherapy agents and, more recently, biological agents, i.e. substances that specifically target the tumour's metabolism.

As a result of the improved survival and tumour control rates and prolonged life expectancies, more and more patients are at risk of experiencing (late) side effects and therapy induced tumours. Side effects resulting from therapeutic radiation exposure can occur early (acute), i.e. within the first 90 days following the start of treatment, or late (chronic), i.e. after a number of months or years (Dörr 2009a). In the case of the latter, the latency period is inversely dependent on the dose (Dörr 2009a). Side effects including changes to the large vessels or coronary heart disease were recently described that occurred years and sometimes even decades (extremely late side effects) after therapy had been completed (Darby et al. 2003, 2010; Dorresteijn et al. 2002; Martin et al. 2005; Schultz-Hector und Trott 2007).

Therapy induced tumours also usually occur years or decades after therapy (Trott 2009). Furthermore, the incidence and type of side effects along with the risk of therapy induced tumours can be modulated through a combination of various antineoplastic chemotherapy agents and biological agents (in the case of biologically targeted therapies).

The primary objective of patient follow-up as part of the radiation therapy quality assurance is the recording of treatment success rates. Additionally however also the impact of treatment must be documented, including all of the side effects that occur over time, i.e. in excess of 5 years, and any therapy induced tumours that occur also need to be documented as they form an essential part of the quality assurance process that applies to radiation therapy. Aftercare is

a basic requirement for early intervention when it comes to treatment protocols indicating increased risks. The impact and side effects also have to be documented in order to optimise existing and new treatment plans, which in turn require comprehensive aftercare measures. Problems concerning follow-up are usually linked to organisation and execution deficits, but may also be traced back to the limited documentation retention period (30 years) and data archiving and evaluation methods.

Implementation of the Guidelines for Radiation Protection in Medicine (RL StrlSch Med) that came into force on 24 June 2002 has shown that they do not sufficiently account for current findings. According to the Guidelines, patients who have received teletherapy or brachytherapy should receive follow-up for 5 years in order to determine and document the effectiveness of treatment and the occurrence of any side effects as only deterministic radiation effects are deemed to be of relevance. The idea behind investigating the outcome of treatment is to "*gain insights into and derive ideal medical benefits for individual patients and enable general comparisons*". This should also include appropriate intervals, "*e. g. 3, 6, 12 months, then annually, for a total of at least 5 years following radiation therapy*" (RL StrlSch Med 2002, no. 7.1.4). In contrast to this, when it comes to nuclear medicine therapy there are no proposals for aftercare intervals or maximum aftercare periods (RL StrlSch Med 2002, no. 6.3.4) as only stochastic radiation effects and long latency periods were assumed to occur, which is not always the case.

The radiotherapist can transfer the patient to a suitable physician who is permitted to carry out certain aftercare measures. The physician is in turn required to submit the results to the radiotherapist as such moves do not entail a transfer of follow-up responsibility from the physician to the radiotherapist (RL StrlSch Med 2002, nos. 6.3.4 and 7.1.4).

The problems that arise during follow-up can be traced back to the fact that until now, it was generally seen as a measure to be used on a patient-by-patient basis in order to monitor the treatment's success rather than an instrument to optimise the therapy in general and conduct quality assurance in connection with late and extremely late effects. In radiooncology, the post-irradiation examination intervals and total follow-up periods set out as examples in the guidelines were often adopted without question. The latest revised version of the guidelines (RL StrlSch Med 2011) no longer defines any specific intervals, hence the need for a cooperation with associations to define specific guidelines for each individual entity of the illness. Follow-up also often entails structural, organisational and, above all, financing problems that need to be solved.

This recommendation is mainly aimed at follow-up of radiation therapy of malignant tumours. In principle, however, the fundamentals behind the proposed follow-up concepts should also be applied to radiation therapy on benign tumours.

2 Terms and definitions

2.1 Deterministic effects of radiation exposure

Radiation therapy always involves a certain volume of normal tissue structure exposed to doses that may well exceed the tolerance range. This applies both to normal tissue within the tumour itself (e. g. vessels) and to normal tissue adjacent to the tumour which are included in the *clinical target volume* (CTV) due to microscopic tumour infiltrate along with tissue that also has to be included in the *planning target volume* (PTV) due to potential positioning inaccuracies or organ movements.

GTV: Gross tumour volume, i.e. detectable volume
CTV: Clinical target volume, i.e. GTV plus volume with suspicious (subclinical) affliction, e. g. safety margin
PTV: Planning target volume, i.e. CTV plus safety margin for movement or changes to the shape of the CTV as well as position changes and technical inaccuracy
TV: Treatment volume to be irradiated with the prescribed dose
IV: Irradiated volume, i.e. volume to be exposed to a significant dose in relation to normal tissue tolerance

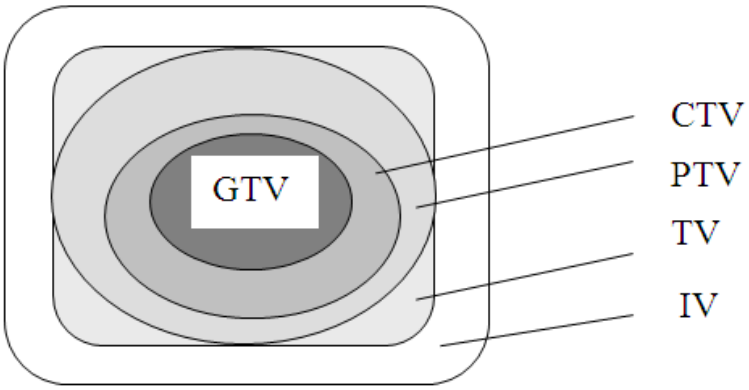

Fig. 1: Target volume definitions as set out by The International Commission on Radiation Units and Measurements (ICRU)

An additional, biologically justified volume classification must be introduced for the present analysis. Aside from the treatment volume defined by the ICRU (**TV**) where the effects of radiation are always to be expected, other "biological" volumes need to be defined: The *stochastic risk volume (SRV)* refers to the volume where stochastic effects (e. g. tumour induction) are to be expected. Also to be taken into consideration are volumes exposed to a dose that exceeds the tissue-specific or organ-specific radiation tolerance of the normal tissue found therein without the mandatory occurrence of any clinical effects; these also include the ICRU's Organs at Risk (OAR). These volumes are hereinafter known as *deterministic risk volumes (DRV).* Here a distinction must be made between (extremely small) volumes exposed to extremely high doses (hot-spot volumes – *hDRV*) and volumes exposed to doses that do not trigger any side effects in the "usual" organs at risk, but could in fact trigger clinically manifest radiation effects in some forms of tissue such as oral mucosa (> 20 Gy). These volumes are known as *nDRV*.

It should be noted that the images below represent the relation of probability distributions among the various radiation effects rather than the spatial relations between the individual volumes. The spatial relations and probability levels need to be investigated on an individual basis. This volume concept has already been used in previous SSK statements (SSK 2011, SSK 2010).

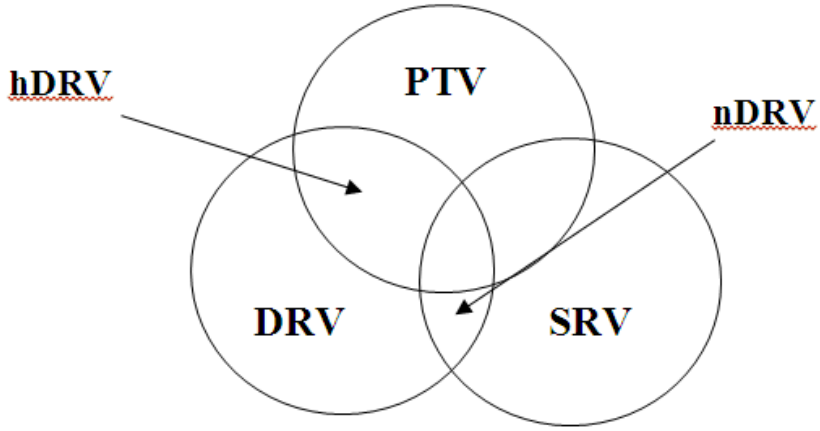

Fig. 2: Biologically determined radiation therapy volumes
As well as the PTV set out by the ICRU, when planning and applying a radiation therapy along with accompanying imaging analyses, volumes have to be included where there is a risk of deterministic radiation effects (deterministic risk volume – DRV) and which are determined by the radiation tolerance of the tissue/organs in the radiation volume and their position in relation to the PTV. Volumes exposed to doses that vastly exceed the PTV's therapeutic dose (hot spots) are hereinafter referred to as hDRV. In addition, volumes must be defined that are subject to doses that do not trigger any side effects in the usual organs at risk, but could in fact trigger clinically manifest radiation effects in some forms of tissue such as oral mucosa (> 20 Gy). These volumes are known as nDRV, i.e. part of the DRV's total volume. Volumes in which stochastic radiation effects are possible (stochastic risk volume –SRV) also have to be taken into account and are defined based on the type of tissue and organs along with their sensitivity in terms of stochastic effects.

The risk of deterministic and stochastic radiation effects can be modified by using antineoplastic chemotherapy agents and biological agents within the scope of targeted therapies.

In nuclear medicine therapy, the exposure level of normal tissue structures depends on the application type, activity and biokinetics of the radiation therapy used. This may of course lead to normal tissue experiencing major exposure. With the systemic application of radionuclides, various dose concepts are used that range from standard activity doses to individual calculations of the activity to be applied based on pre-therapeutic dosimetry. To this end, the dose for individual organs based on the activity applied are currently determined using the MIRD (Medical Internal Radiation Dose) concept (Bolch et al. 2009) or Monte Carlo-based calculation method together with scintigraphically determined whole-body distribution over time, knowledge of physical properties, tracer kinetics and the dose amounts of source and target structures derived therefrom.

Both the patient and physician accept the fact that a promising radiation therapy is always associated with a certain risk of side effects. However, these risks can only be estimated if every patient is subjected to systematic follow-up at relevant intervals over an appropriate period of time.

2.1.1 Early side effects

By definition, early (acute) side effects occur up to 90 days after radiation therapy has commenced and are often observed in turn-over tissue such as epithelia or bone marrow in which physiological cell loss is usually balanced out by constant cell renewal (Dörr 2009a,

Dörr und Herrmann 2002). Exposure to radiation leads to disruptions in cell production while cell loss continues irrespective of the treatment. This increasing lack of cell replenishment eventually leads to a total loss of functional cells. This can be seen in the form of epithelia ulcerations, bone marrow atrophy in the haematopoietic system and loss of peripheral function cells in the blood (leukopenia, anaemia). In addition, there may also be unusually early reactions to radiation involving another pathogenesis, e. g. early reaction of the lungs or urinary bladder to radiation (Dörr und Herrmann 2002).

Early side effects increase drastically with a reduction of the total treatment period (accelerated radiation therapy), but only drop slightly with a reduction in the dose per fraction (hyperfractionation) or dose rate (see 2.1.5).

2.1.2 Late side effects

Late side effects resulting from radiation can occur in any organ or tissue. This is based on a complex interaction that takes place between various cell populations where the connective tissue cells' reaction to radiation becomes increasingly important with the increased formation of collagen and capillary endothelial cells with subsequent capillary loss and therefore impedes the supply of downstream regions (Dörr 2009a). Reactions also regularly occur in the organs' own (parenchyma) cells. While these side effects may no longer seem to occur in some organs, e. g. the intestine, after several years they may occur relatively early or even as late as a few decades later in other organs, e. g. the urinary bladder (Jung et al. 2001). What is of significance here is the fact that the latency period between radiation exposure and manifestation of chronic side effects is inversely dependent upon the dose in the irradiated tissue volume (Dörr 2009a).

These typically late side effects can be reduced by decreasing the dose per fraction or effectively reducing the dose rate. A reduction of the total treatment period does not generally have any influence on this, however (see 2.1.5).

Alongside these typically late reactions there is a range of other radiation effects with specific atypical and pathophysiological mechanisms that represent a chronic manifestation. These include, for example, the reaction of the lens of an eye (radiation cataract) or the breasts of prepubescent girls to radiation.

Following therapy with open radionuclides, late side effects may occur depending on the therapeutic biodistribution of the radiopharmaceutical and resulting dose distribution. They are often caused as a result of nuclide absorption by parenchymal cells (e. g. thyroid gland or kidney). The most common and often intended late effect in nuclear medicine resulting from therapy is hypothyroidism after using radioiodine therapy to treat problems with the thyroid gland. Following systemic application of radiopharmaceuticals, late effects may occur in tissue that was not adjacent to the treatment's target structures, e. g. renal failure following oncological radiopeptide therapy or changes to the lung resulting from hepatopulmonary shunts when performing selective intraarterial radiation therapy (SIRT) on liver tumours.

2.1.3 Consecutive late effects

In some organs and tissue, the surface epithelium acts as a form of protection against mechanical and/or chemical stimuli. Examples of this include the intestine, oral mucosa, the urogenital tract, the lungs and the skin (in sensitive areas). Within the scope of early reaction, this protection barrier is damaged and, depending on the extent of the symptoms (severity, duration), can lead to secondary damage to the vessels' connective tissue, i.e. the target structures for chronic reactions to radiation. Together with an early reaction, this mechanism can have an extremely negative impact on chronic reactions to radiation and is therefore

known as the consecutive radiation effect (Dörr und Hendry 2001, Dörr 2009a). What is important here is that the consecutive aspect of the late effects reacts in the same way from a radiobiological perspective as with an early reaction when it comes to dose fractioning and/or changing the dose rate and total period of exposure.

2.1.4 Extremely late effects

The survival rates and life expectancies achieved today thanks to technical progress, the continued development of existing therapies and the establishment of new therapies lead to an increase in the need to focus on extremely late effects. Side effects have recently been described within the scope of lifelong follow-up of radiation therapy patients that only occur after a number of years and even decades after treatment has been completed. From now on these are known as extremely late side effects and include heart disease that can occur and must be monitored when irradiating mammary carcinomas on the left-hand side (Darby et al. 2010; Schultz-Hector und Trott 2007; Mc Gale et al. 2011) along with late enlargements or stenoses of arteries or an increased manifestation of atherosclerotic changes (Brown et al. 2005; Dorresteijn et al. 2002; Plummer et al. 2011; Stewart et al. 2010). In nuclear medicine this includes late hypothyroidism following radioiodine therapy.

2.1.5 Influencing factors

Deterministic radiation effects may be induced by certain radiation exposure factors (Steel 1997; Withers et al. 1986; Dörr 2009a, b). In principle, an increase in radiation dose leads to an increased manifestation of side effects. In general the administration of antineoplastic chemotherapy agents also results in an increase in the prevalence of early side effects; the influence they have on late side effects is generally unclear, however, but seems to be closely linked to the tissue that has been irradiated. Some antineoplastic chemotherapy agents have a known side-effect potential (e. g. cisplatin: ototoxicity, nephrotoxicity; anthracyclines: cardiotoxicity; bleomycin: pulmonary toxicity). A lot of biological agents show early side effects, especially in the skin (Ulrich et al. 2008), but little is currently known about the chronic side effects of biological agents.

A reduction in the *dose per fraction* for hyperfractionated treatment protocols (teletherapy) or *dose rate* (brachytherapy, nuclear medicine therapy) positively reduces the incidence of chronic side effects. On the other hand, a reduction in the *total treatment period* for accelerated teletherapy records has a negative impact on the occurrence of early radiation effects. Here it is important to point out that in contrast to the above, the consecutive components of chronic radiation effects are assumed to be dependent upon the total treatment time and not the dose per fraction or dose rate.

The dependency of side effects on the irradiated *volume* of the respective organ is far more complex (Dörr et al. 2009c) as it requires a distinction between organs that are sensitive to dose peaks (hot spots – hDRV) such as the spinal cord or gastrointestinal tract (“tubular” organs) and organs where the overall volume is exposed to irradiation exceeding the tolerance limit such as the lungs or liver (“parallel” organs). As a result, tubular organs are of minor importance as dose peaks can largely be avoided in normal tissue when using modern radiation therapy techniques. On the other hand, new radiation methods and their associated imaging processes (e. g. image guidance) expand the volume exposed to low and medium doses (the latter may exceed the tolerance limit), i.e. DRV and nDRV, which may of course impact the risk of side effects.

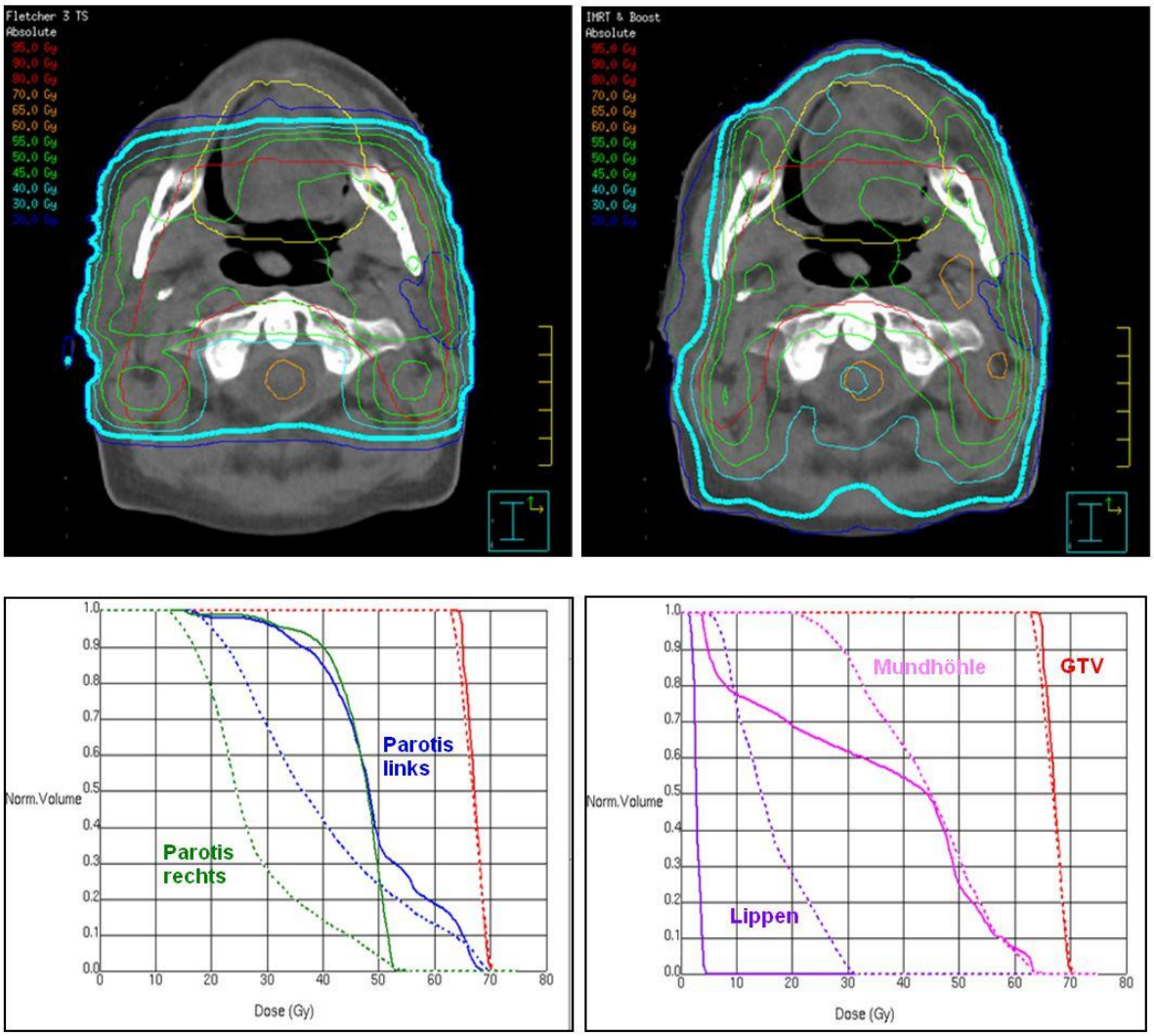

Fig. 3: Conformal radiation therapy (IMRT – radiation therapy plan above on the right-hand side) of a head and neck tumour compared to conventional therapy (radiation therapy plan below on the left-hand side).
By adjusting the PTV so that it is almost identical to that of the GTV, the right parotid gland can be largely protected (left dotted line in DVH: IMRT, solid line: conventional plan), which helps to reduce radiogenic dryness in the mouth (xerostomia). This causes an expansion of the nDRV, which in turn leads to a significant proportion of the oral mucosa (DVH on the right) and, in particular, the labial mucosa from being exposed to doses during IMRT that exceed the 20 Gy tolerance dose (DVH on the right). This in turn causes extensive and more intensive radiogenic oral mucositis, particularly in and around the lips, which is of major detriment to the patient's overall wellbeing.

Currently there is a lack of knowledge surrounding the dependency of extremely late radiation effects on dose, treatment protocols, irradiated volume, or combination with other forms of treatment.

After systemic therapy involving open radionuclides, the anticipated extent of radiation effects depends on the individual organ dose. Suitable measures prior to or during the application of the radionuclide may impact on the tracer's biodistribution and minimise both organ tissue retention and thus the risk of late effects. This includes the administration of recombinant rTSH during radioiodine therapy for thyroid gland tumours which is intended to

reduce the whole-body dose, and the co-infusion of amino acids during radio peptide therapy to prevent radiogenic kidney damage.

2.2 Radiation-induced tumours

2.2.1 Direct effects

The current state of knowledge for stochastic radiation effects, which include the formation of mutations or induction of tumours, is that there is no minimum dose threshold, meaning that extremely small doses could also trigger such effects. The exact extent of dose-effect relations is currently a somewhat controversial topic (Brenner et al. 2003). A linear dose-effect relationship is assumed for extremely small doses of just a few Gy. Findings from conventional fractionated radiation therapy show that there is a rise in the incidence of radiation-induced tumours with doses of 2 to 3 Gy (Dörr und Herrmann 2002).

The relative risk of new illnesses and the mortality rate resulting from radiation-induced secondary tumours following conventional fractionated radiation therapy as well as nuclear medicine therapy is between 1 and 2 for follow-up periods of less than 10 years. However, the absolute rates (incidence or mortality) are generally well below 1 % a year, i.e. very low. This was seen, e. g. when comparing radiation therapy for patients suffering from prostate or mammary carcinoma with patients that only had surgery (e. g. Brenner et al. 2000; Darby et al. 2005; Kleinerman et al. 1995). Longer follow-up periods, i.e. > 10 years, provide somewhat higher values (e. g. Travis et al. 2005).

2.2.2 Indirect effects

Alongside the direct cell transformation as a result of ionising radiation, secondary tumours may develop in some organs, e. g. the bladder or rectum, due to chronic deterministic effects (proliferative inflammations) in the high-dose volume DRV (Baxter et al. 2005). Here the relative risk could easily be much higher than 2 (Kleinerman et al. 1995). There is absolutely no indication of how high the "indirect" stochastic risk is in the hDRV. Very small yet significant volumes of just a few cubic millimetres of extremely high doses are administered there and trigger chronic changes of extremely small volume. There is currently no data available with regard to the dependence of volume on indirect stochastic radiation effects.

Apart from these few examples, the wide range of data collection and analysis methods available provide us with very little information regarding tumour induction – hence the need for quality assurance when it comes to follow-up concepts.

3 Follow-up period and intervals

3.1 Follow-up period

According to the Guidelines for Radiation Protection in Medicine from 2002 (RL StrlSch Med 2002, no. 714), patients who have received radiation therapy should be observed for a total of five years with follow-up intervals of, e. g. "3, 6, 12 months, then annually". In contrast to this, there are neither follow-up intervals nor a maximum follow-up period in place for nuclear medicine therapy (RL StrlSch Med 2002, no. 6.3.4).

The five-year limit on the follow-up period that applies to tumour radiation therapy was recommended by the SSK in 1998 (SSK 1998). The basis for this recommendation was a review within the scope of a habilitation thesis on the latency period of the side effects of radiation involving > 500 radiation therapy patients in the former German Democratic

Republic (Arndt 1985). Here it was assumed that this “five-year tumour control rate” would also sufficiently indicate the effectiveness of radiation therapy together with side effect rates.

However, more recent studies show that most local recurrances that occur with a number of tumours (e. g. in the lungs, head and neck, and brain) are in fact indicative of treatment failure when they occur after one to five years. This period may be somewhat later with, e. g. mammary and prostate carcinoma or after multimodal therapy such as rectal carcinoma.

Several studies also show that side effects due to radiation exposure can also occur after a five-year follow-up period. One is the evaluation of side effect frequencies observed by Jung (Jung et al. 2001) which clearly shows that the risk of side effects remains constant for the remainder of the (former) patient’s life, meaning that there is no justification for limiting follow-up to five years. The analysis carried out by Jung et al. (Jung et al. 2001) matches various other publications (e. g. Dörr 2009a) in that it shows that the period of time that elapses until a side effect arises depends on the respective tissue or organ.

There are very few investigations that provide meaningful insights into the manifestation of side effects as a result of combining radiation therapy with chemotherapy agents or even biological agents ("biologically targeted therapies").

It is only possible to ensure that the effects and, in particular, side effects of radiation exposure are correctly documented if every patient is monitored for at least the same period of time as the documentation retention period (30 years). Should any radiation effects be observed that fit to a spectrum to be defined by the scientific associations (see below) the follow-up period and of course the documentation retention period need to be prolonged accordingly.

Quality assurance of radiation treatment can only be performed if the effects and side effects of every patient treatment are documented and analysed. This is mainly the responsibility of the physician with relevant radiation protection expertise who administers the therapy. The physician should always obtain the required information and aftercare findings in order to enable best-possible therapeutic benefits for individual patients and to gain insights into treatment methods. As a result, the party responsible for radiation protection should make sure that the physician with relevant radiation protection expertise documents the effects and side effects of radiation therapy by performing checks at appropriate intervals. The checks should be carried out by the physician or someone else charged with the task by the physician and should include any external findings, observe interdisciplinary institutions (e. g. tumour centres, cancer register) and guidelines or orientation aids relating to checks while observing the correct timeframe. Any required treatment can then be administered based on these findings. The maximum data collection period is based on the retention periods set out in § 85 of the German Radiation Protection Ordinance (StrlSchV) and is to be prolonged should any side effects occur.

Especially when irradiating malignant tumours, the check-up intervals need to be adapted to the prognosis of the illness, the risk of manifestation, potential side effects and their typical development over time. The patient must be provided with sufficient support until the early effects of radiation subside. Tumour check-ups and late effects of radiation are to be documented for at least three and five years after radiation therapy has been completed, but must always account for late and extremely late side effects.

A legal basis is required to implement the above points for follow-up as part of the quality assurance process in order to ensure that findings can be accounted for in the corresponding S3 guidelines put in place by the Association of the Scientific Medical Societies in Germany (AWMF).

3.2 Follow-up intervals

The time at which the effects of radiation occur clearly depends on the organ or tissue that has been irradiated (Dörr 2009a; Jung et al. 2001), the location of the tumour and surrounding organs at risk, the treatment schedule following nuclear medicine therapy, and the type of radiopharmaceutical used as well as its individual biokinetics. The time at which recurrances occur is influenced by the tumour biology and treatment plan, which is why it rarely makes sense to define general follow-up intervals for all tumour entities and symptoms indicating the need for treatment. Follow-up intervals should in fact be determined on the basis of potentially affected organs with new therapy strategies also taking any new potential risk tissue into account.

These check-up intervals within the scope of structured follow-up plans need to be coordinated by experts in their respective discipline; hence the recommendation that the scientific associations involved draw up standardised follow-up programs for all radiation therapy indications and then update them at regular intervals based on the current state of therapy strategy development. There needs to be a minimum aftercare standard that applies across the board and should include check-ups during the early phase and after 3 and 5 years at the least after administering radiation therapy for tumours. There should also be structures and mechanisms in place to monitor and document developments in the long term.

4 Follow-up organisation

The institution administering treatment is to assume responsibility for ensuring that the follow-up obligation is complied with. The SSK does however acknowledge that patient numbers, logistical hurdles and time constraints all make it very difficult to provide personalised aftercare for all radiation therapy patients only at the institution that administers treatment. This also applies to radiooncology and nuclear medicine, which is why alternative concepts and plans need to be drafted where the institution administering treatment is responsible for implementing them. The following section describes the potential options available in this regard.

4.1 Aftercare provided by the institution administering treatment

In order to enable the institution administering treatment to provide follow-up, patients need to be grouped based on their risk of encountering side effects and recurrance. The follow-up intervals applied also need to be based on this risk. Every patient should be informed about the importance of follow-up and the necessity to clarify any findings that could be related to their radiation therapy with the institution that provided the treatment. The institution providing treatment must be responsible for regularly monitoring patients with a moderate risk of experiencing undesired effects of radiation. Any other institutions or physicians involved in the follow-up process should also be informed with regard to any findings. Here it should be pointed out that post-irradiation examinations and follow-up of patients are both a compulsory part of the radiation therapy process.

Patients with a high risk of encountering undesired effects of radiation, e. g. after having been treated using recently introduced therapy plans, after having been subjected to dose-escalated therapy or aggressive radiochemotherapy, or after having been treated with new radiopharmaceuticals, have to receive follow-up from the institution providing treatment because only the physician in charge of the therapy can ensure that treatment was effective.

On top of that, only the physician in charge of therapy can identify and document all of the side effects so that these findings can then be adopted into general follow-up plans.

In the case of patients with a moderate risk of encountering undesired effects resulting from radiation, the institution administering treatment is responsible for making sure that they are regularly examined and monitored. This may involve contacting the patient and enquiring about their health and any potential side effects, e. g. in the form of a structured telephone interview or standardised questionnaire to be drafted and regularly updated by scientific associations. Should any side effects occur or if any such side effect is suspected, the patient must be summoned to attend a personal post-irradiation examination at the institution. If the post-irradiation examination is performed by some other institution or a different physician, they can also interview the patient (see below).

Both physicians that provide follow-up and patients with a known low risk of encountering side effects, e. g. following the application of sufficiently established, generally recognised treatment protocols, must be made aware that they need to inform the institution that provided the radiation therapy if there is a suspicion of the patient suffering a recurrance or side effects or any other findings that could be related to radiation therapy. In such instances, these patients and their physicians have to be contacted on a regular basis, as is the case with patients at moderate risk, but at greater intervals.

4.2 Transferring follow-up duties

If the post-irradiation examination is performed by some other institution or a different physician, they can also provide the relevant information rather than directly querying patients with a low or moderate risk. The transfer of follow-up to others also has to be documented and the institution administering treatment still retains responsibility. It cannot be assumed that other institutions will provide feedback if there are no obvious side effects or unclarified findings related to radiation therapy, which is why the institution administering treatment needs to ensure reciprocal feedback on a regular basis, either in the form of a telephone call or by requiring the institution that provides aftercare to enter their findings into a database. In the case of the latter, regular checks must be performed to ensure that the information entered is complete.

5 Documenting effects and side effects - Databases

The detection and documentation of effects and side effects resulting from radiation therapy primarily serve to ensure treatment quality at the administering institution. The SSK also recommends that late and extremely late effects of radiation therapy and any secondary tumours be added to the epidemiological and clinical register. Institutions should have standardised data entry processes when managing their databases in order to be able to compare results with those from other institutions. It must also be possible to compare results with those in the epidemiological registers. This should be seen as an additional requirement alongside the administering institution’s obligation to archive relevant data and documentation.

Patient-related data must be retained and patient related (i.e. the duty to delete data needs to be revoked). Furthermore there is still a need to conduct research into data transferability between various documentation systems and in order to optimise records.

5.1 Documenting the outcome of treatment

With malignant diseases, the effect of treatment must be documented based on the following parameters: local tumour investigations and the absence of recurrances, disease-related survival rates and general survival rates. These parameters are only partly present and available in the tumour register databases, meaning that institutions need to collect and document them separately.

5.2 Documenting side effects

The side effects of radiation therapy need to be documented in a structured manner. The first problem encountered in this regard is the documentation system itself. General documentation records (Seegenschmiedt 1998) such as the RTOG/EORTC (Radiotherapy and Oncology Group/European Organisation for Research and Treatment of Cancer), the various versions (currently 4.0) of the CTC AE (Common Terminology Criteria for Adverse Events) of the National Cancer Institutes in the USA, or the LENT/SOMA scale (Late Effects in Normal Tissue/Subjective Objective Management Analysis) categorise side effects into 6 levels (see Table 1).

Table 1: Side-effect levels of radiation therapy

Level	Description
0	No change
1	Few side effects, no specific treatment necessary
2	Moderate side effects requiring outpatient treatment
3	Significant side effects often requiring inpatient treatment
4	Life-threatening situations
5	Death resulting from side effects

There are a number of organ-specific scales of side-effects here, some of which can have several levels for the same organ. In order to systematically document side effects so that they can be compared with one another, care must be taken to ensure that documentation can be transferred between systems as this is currently not the case. In terms of transferring data from one documentation system to another, prospective studies should be performed with regard to the retrospective analysis of side-effect rates.

One way of standardising documentation related to the side effects of radiation therapy is to use one (electronic) system that can be made available to all institutions involved in the treatment process. If follow-up results are then transferred to a different physician/institution, documentation can still be performed via a corresponding server system. It must also be possible to compare results with those in the cancer and clinical registers.

Databases on side effects should primarily be managed and updated by the institutions administering treatment in a decentralised manner. A standardised system would however enable the various institutions to merge their data and allow multicentric analyses that could be used in scientific investigations. Solutions such as these could also document factors relevant to the manifestation of side effects such as chemotherapy plans, genetic predispositions, chemical noxa, etc.

5.3 Documenting secondary tumours

Secondary tumours that occur during clinical follow-up cannot always be documented by the administering physician due to the long latency periods. In addition, secondary tumours are often diagnosed and treated by other disciplines, which is why there must be an opportunity to compare data, including the radiation treatment itself, with secondary tumour data in cancer registers. Legal guidelines therefore need to be drawn up in order to achieve this.

6 Implementing the follow-up concept

Patient follow-up is an essential and unseparatable part of the treatment concept. With radiation therapy, follow-up helps to ensure treatment quality and is therefore fundamental in terms of justifying indications.

The structural, staffing and financial requirements for proper follow-up also need to be clarified and documented, and this also includes appropriate cost reimbursements and funding of suitable research plans during the design phase.

Bibliography

Arndt 1985 — Arndt D. Die gutachterliche Bewertung von Komplikationen im Zusammenhang mit medizinischer Strahlenanwendung in der DDR. Ergebnisse der zentralen Begutachtung im Zeitraum 1/68-3/84 und Ableitung von Begutachtungskriterien. Habilitationsschrift, Akademie für ärztliche Fortbildung der DDR, Berlin-Lichtenberg, 1985.

Baxter et al. 2005 — Baxter NN, Tepper JE, Durham SB, Rothenberger DA, Virnig BA. Increased risk of rectal cancer after prostate radiation: a population-based study. Gastroenterology 2005; 128(4): 819-824.

Bolch et al. 2009 — Bolch WE, Eckerman KF, Sgouros G, Thomas SR. MIRD Pamphlet No. 21: A Generalized Schema for Radio-pharmaceutical Dosimetry - Standardization of Nomenclature. J Nucl Med 2009; 50: 477-484.

Brenner et al. 2000 — Brenner DJ, Curtis RE, Hall EJ, Ron E. Second malignancies in prostate carcinoma patients after radiotherapy compared with surgery. Cancer 2000; 88(2): 398-406.

Brenner et al. 2003 — Brenner DJ, Doll R, Goodhead DT, Hall EJ, Land CE, Little JB, Lubin JH, Preston DL, Preston RJ, Puskin JS, Ron E, Sachs RK, Samet JM, Setlow RB, Zaider M. Cancer risks attributable to low doses of ionizing radiation: assessing what we really know. Proc Natl Acad Sci U S A 2003; 100(24): 13761-13766.

Brown et al. 2005 — Brown PD, Foote RL, McLaughlin MP, Halyard MY, Ballman KV, Collie AC, Miller RC, Flemming KD, Hallett JW. A historical prospective cohort study of carotid artery stenosis after radiotherapy for head and neck malignancies. Int J Radiat Oncol Biol Phys 2005; 63: 1361-1367.

Darby et al. 2003 — Darby S, McGale P, Peto R et al. Mortality from cardiovascular disease more than 10 years after radiotherapy for breast cancer: Nationwide cohort study of 90 000 Swedish women. BMJ 2003; 326: 256–257.

Darby et al. 2005 — Darby SC, McGale P, Taylor CW, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. Lancet Oncol 2005; 6(8): 557-565.

Darby et al. 2010	Darby SC, Cutter DJ, Boerma M, Constine LS, Fajardo LF, Kodama K, Mabuchi K, Marks LB, Mettler FA, Pierce LJ, Trott KR, Yeh ET, Shore RE. Radiation-related heart disease: current knowledge and future prospects. Int J Radiat Oncol Biol Phys 2010; 76: 656-665.
Dorresteijn et al. 2002	Dorresteijn LD, Kappelle AC, Boogerd W et al. Increased risk of ischemic stroke after radiotherapy on the neck in patients younger than 60 years. J Clin Oncol 2002; 20: 282-288.
Dörr 2009a	Dörr W. Pathogenesis of normal tissue side effects. In: Joiner M, Van der Kogel A (Hrsg.). Basic Clinical Radiobiology, 4th Edition, Kap. 13; Hodder Arnold, London 2009, 169-190.
Dörr 2009b	Dörr W. Time factors in normal tissue responses to irradiation. In: Joiner M, Van der Kogel A (Hrsg.). Basic Clinical Radiobiology, 4th Edition, Kap. 11; Hodder Arnold, London 2009, 149-157.
Dörr et al. 2009c	Dörr W, Van der Kogel AJ. The volume effect in radiotherapy. In: Joiner M, Van der Kogel (Hrsg.). Basic Clinical Radiobiology, 4th Edition, Kap. 14; Hodder Arnold, London, 2009; 191-206.
Dörr und Hendry 2001	Dörr W, Hendry JH. Consequential late effects in normal tissues. Radiother Oncol 2001; 61: 223-231.
Dörr und Herrmann 2002	Dörr W, Herrmann Th. Second primary tumors after radiotherapy for malignancies. Treatment related parameters. Strahlenther Oncol 2002; 178: 357-362.
Dörr und Herrmann 2009	Dörr W, Herrmann, Th. Frühe Strahlenveränderungen der Gewebe. In: Bamberg M, Molls M, Sack H (Hrsg.). Radioonkologie. Band 1: Grundlagen; 2. Aufl. W. Zuckschwerdt Verlag GmbH, Germering/München, 2009; 302-309.
Jung et al. 2001	Jung H, Beck-Bornholdt HP, Svoboda V, Alberti W, Herrmann T. Quantification of late complications after radiation therapy. Radiother Oncol 2001; 61(3): 233-246.
Kleinerman et al. 1995	Kleinerman RA, Boice JD Jr, Storm HH, Sparen P, Andersen A, Pukkala E, Lynch CF, Hankey BF, Flannery JT. Second primary cancer after treatment for cervical cancer. An international cancer registries study. Cancer 1995; 76(3): 442-452.
Martin et al. 2005	Martin JD, Buckley AR, Graeb D et al. Carotid artery stenosis in asymptomatic patients who have received unilateral head and neck irradiation. Int J Radiat Oncol Biol Phys 2005; 63: 1197 - 1205.

McGale et al. 2011 McGale P, Darby SC, Hall P, Adolfsson J, Bengtsson NO, Bennet AM, Fornander T, Gigante B, Jensen MB, Peto R, Rahimi K, Taylor CW, Ewertz M. Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. Radiother Oncol 2011 Aug; 100(2):167-75.

Plummer et al. 2011 Plummer C, Henderson RD, O'Sullivan JD, Read SJ. Ischemic stroke and transient ischemic attack after head and neck radiotherapy: a review. Stroke 2011, 42: 2410-2418.

RL StrlSch Med 2002 Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit (BMU): „Strahlenschutz in der Medizin" Richtlinie nach der Strahlenschutzverordnung, 2002, GMBl 2003, S. 227

Schultz-Hector und Trott 2007 Schultz-Hector S, Trott KR. Radiation-induced cardiovascular diseases: is the epidemiologic evidence compatible with the radiobiologic data? Int J Radiat Oncol Biol Phys 2007; 67: 10-18.

Seegenschmiedt 1998 Seegenschmiedt MH. Nebenwirkungen in der Onkologie. Internationale Systematik und Dokumentation. Springer, Berlin Heidelberg New York, 1998.

SSK 1998 Strahlenschutzkomission (SSK): Nachsorge für Patienten nach Strahlenbehandlung. Empfehlung der Strahlenschutz-komission, BAnz Nr. 144, S. 11450, 1998.

SSK 2010 Strahlenschutzkommission (SSK): Strahlenhygienische Anforderungen an IGRT (image guided radiotherapy/ bildgeführte Strahlentherapie). Empfehlung der Strahlen-schutzkommission, BAnz Nr. 68, S. 1599, 2011.

SSK 2011 Strahlenschutzkommission (SSK): Strahlenhygienische Anforderungen an die hochkonformale Strahlentherapie. Stellungnahme der Strahlenschutzkommission, verabschiedet in der 248. Sitzung der SSK am 14./15.04.2011

Steel 1997 Steel GG. Clonogenic cells and the concept of cell survival. In: Steel GG, editor. Basic Clinical Radiobiology. 2. Auflage, London New York, Arnold Publ., Kap. 6, 40-51, 1997.

Stewart et al. 2010 Stewart FA, Hoving S, Russell NS. Vascular damage as an underlying mechanism of cardiac and cerebral toxicity in irradiated cancer patients. Radiat Res 2010; 174: 865-869.

StrlSchV 2002 Verordnung über den Schutz vor Schäden durch ionisierende Strahlen (Strahlenschutzverordnung – StrlSchV) vom 20. Juli 2001, (BGBl. I S. 1714), geändert durch Artikel 2 der Verordnung vom 18. Juni 2002 (BGBl. I S. 1869, 1903).

Travis et al. 2005	Travis LB, Hill D, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, Glimelius B, Andersson M, Pukkala E, Lynch CF, Pee D, Smith SA, Van't Veer MB, Joensuu T, Storm H, Stovall M, Boice JD Jr, Gilbert E, Gail MH. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. J Natl Cancer Inst 2005; 97(19): 1428-1437.
Trott 2009	Second cancers after radiotherapy. In: Joiner, M, Van der Kogel A (Hrsg.). Basic Clinical Radiobiology, 4th Edition, Kap. 25; Hodder Arnold, London 2009, 339-352.
Ulrich et al. 2008	Ulrich J, Hartmann JT, Dörr W, Ugurel S. Skin toxicity of anti-cancer therapy. J Dt Dermatol Gesellsch 2008; 6: 959-977.
Withers, et al 1986	Withers HR. The four R's of radiotherapy. In: Lett, Adler (Hrsg.). Advances in radiation biology. 5. Auflage. New York Academic Press 1975, 241-271.