Chapter 15
"Radiation Effects" in Patient Treatment

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Introduction

Radiation therapy, i.e. treatment with ionizing radiation, is a key component of modern tumor therapy. In Germany, about 450,000 new cases of cancer are currently diagnosed each year. Just under half of the patients receive radiation therapy during the course of their disease. In many cases, radiation therapy is curative, and it is an essential component of the treatment plan in more than half of "cancer cures." And discomfort can be effectively alleviated, even in patients who cannot be cured.

At the time of exposure, ionizing radiation is "soundless, painless and unspectacular." Its effect shows up with a delay in biological systems. The interval and the extent of the effect depend on the particular organ, the dose and the irradiated volume as well as individual factors. Only over the long term, after years and sometimes decades, does failure becomes apparent—as a tumor recurrence, severe consequences due to the tissue tolerance threshold being exceeded or tumor induction. The public is very aware of general "radiation risks," primarily with regard to the debate over nuclear power, and the reason for avoiding those risks is evident.

However, the present article addresses the special situation of using ionizing radiation intentionally for medical benefit. Effectiveness (the desired effect is attained) and efficacy (the use of resources and undesired consequences are minimized) are in the foreground here.

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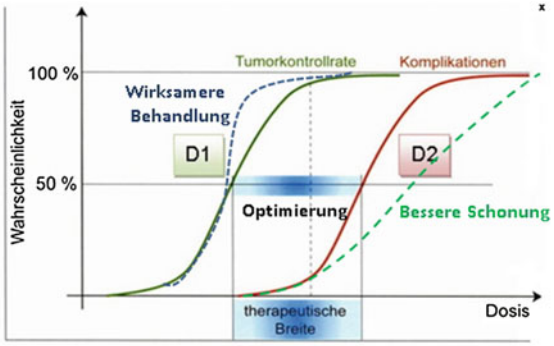


Wahrscheinlichkeit	Probability
Tumorkontrollrate	Tumor control rate
Komplikationen	Complications
Wirksamere Behandlung	More effective treatment
Optimierung	Optimization
Bessere Schonung	Improved protection
therapeutische Breite	Therapeutic scope
Dosis	Dose

Fig. 15.1 Dose-response relationship of radiation therapy; for translation of German expressions, see table given in figure

The sigmoidal dose-response relationship of radiation therapy, with opposing effects of benefit and harm, has been paradigmatically described by Holthusen (1936) (Fig. 15.1).

As a rule, then, risk management means optimizing the relationship between irreconcilably competing risks (cure and side effect).

"Uncertainties" as a characteristic of risk exist because of the interval between exposure and observable biological effect, differing individual sensitivity (on the part of both patients and tumor) and the complexity of the radiation therapy chain and interdisciplinary tumor treatment as a whole.

Risk management thus faces various challenges and must also adapt to rapid medical development.

Extensive statutory regulations, namely the German Radiation Protection Ordinance and the EU Council Directive (2013/59/Euratom), contain provisions for the protection of the population in general as well as patients. These provisions are set forth more specifically in national guidelines and in recommendations, for example, those of the German Radiation Protection Committee (Strahlenschutzkommission, SSK), and reconciled with medical progress and reconsidered if necessary.

Radiation protection for patients is set forth in two main requirements:

- Medical exposure to radiation must be justified.
- The extent of the exposure must be as low as possible to achieve the desired objective.

Risk management must therefore address two different areas:

(1) General risk/benefit ratio

   a. What is the quality of the result of medical radiation treatment?
   b. Are there technological developments or new medical findings that make radiation treatment more effective and/or better tolerated?
   c. Are there developments that avoid the use of ionizing radiation while maintaining the same degree of effectiveness?
   d. Are there interactions between modalities (primarily radiation therapy and medications) that influence effectiveness in an unforeseen way?

(2) Individual patients' risk/benefit ratio

   a. Is treatment potential being optimized?
   b. Are individual particularities adequately recognized?
   c. Will treatment failure or severe side effects be recognized in time to be able to possibly counter them or prevent similar developments in the future?

From the patient's point of view, there are three risks:

- Treatment that is not appropriate for the disease situation brings about no benefit.
- Under-dosed treatment leads to disease recurrence.
- Treatment that is too intensive leads to unnecessary side effects.

General Relationship Between Benefit and Harm

During the author's thirty years of professional experience, radiation therapy has changed in unimaginable ways. It's come a long way from setting simple fields in a patient to precision radiation treatment with tolerances of just a few millimeters. The effects of multimodal imaging, compute-supported planning of non-homogeneous dose distributions, dose escalation and changed target-volume plans cannot be precisely measured on an individual basis. The current consensus that medical progress must be proven in an evidence-based fashion using randomized studies is very strongly shaped by the medication development process. This only partially meets the special requirements of radiation medicine. Because of a lack of support or resistance to making appropriate instruments available, relevant questions are not conclusively investigated.

Technological process that makes possible the minimization of radiation doses outside of the target volume and a dosage increase for tumors that have so far been

poorly treatable can be described in such an obvious and quantitative way that it needs not be proven in patient studies or cannot/must not be investigated in randomized studies. Implementation into routine clinical practice occurs gradually and continuously. However, this does not solve the question of "optimal" use and real benefit.

Effectiveness and significance for patients are revealed as quality of care across geographical areas and over time. Long-term cures and tolerability (ultra-late side effects >10 years, secondary tumor risk) are likewise not investigable in prospective studies due to their latency periods and relative rarity (patient numbers, follow-up observation, therapy standardization), as the preferred study of prostate cancer is currently demonstrating in a painful way.

Recording long-term courses in registries by means of suitable parameters would probably be more expedient. Relevant prerequisites have been created by the early cancer detection and cancer registry law (Krebsfrüherkennungs- und -registergesetz, KRFG; 9 April 2013). However, there are still significant deficits in implementation that affect radiation medicine in particular: limited recording period, no reliable reporting mechanism, lack of interlinking with non-tumor-related data that would be important to morbidity and risk constellations.

However, the problems go above and beyond just the effects of radiation, as cancer therapy is increasingly carried out in an inter-disciplinary and multimodal fashion. Ever more frequent warnings from the pharmaceutical industry, because of unexpected severe and very severe complications due to the interaction of new targeted substances with radiation therapy, are a clear sign of inadequate risk management or learning that takes place after the damage has already occurred.

There is currently an almost exponential increase in new drugs that intervene in central cellular homeostasis signaling pathways, which are also essential for modulating the effects of radiation.

This differs fundamentally from tumor chemotherapy, with which extensive experiences have already been made, and which involves a relatively small number of substances. The number of new medications and the short half-life until the development of imitators/successor substances make valid assessment difficult. These new therapeutic agents usually require ongoing medication, unlike classical chemotherapy, meaning that the probability of coinciding with radiation therapy is greater.

In practice, special problems and a high potential risk of interactions between ionizing radiation and drug therapy of tumors arise for the following reasons:

(1) Sequential use by different treatment providers;
(2) Comorbidities in individual patients intensify or mask interactions;
(3) This can lead to over-reporting (individual case observation) as well as to
(4) Under-reporting due to a lack of experience on the part of the physician confronted with the complication and a low number of cases;
(5) Unintended combination, because of therapeutic changes that become necessary in the course of the condition.

In this context, the recall phenomenon (asynchronous occurrence of a reaction with application of a second modality) is especially critical.

However, interaction with radiation therapy is not part of regulatory drug approval.

The relevant studies take place too late, are not funded and cannot address the particular problem of unplanned and metachronous combination. The significance increases with intensification of many tumor therapies, increasing multimodality and diversification of drug therapy in particular (including immunotherapeutic agents with delayed and prolonged activity).

Individual Patient Relationship Between Benefit and Side Effect

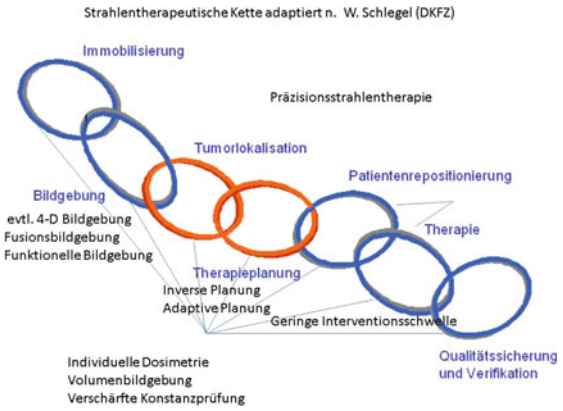
When journalists in Hamburg uncovered a cluster of severe complications after a specific radiation therapy plan in the Eppendorf University Hospital, it soon became clear that lack of follow-up care in particular, and/or a lack of feedback from affected patients, were the reasons why a novel, complication-ridden therapy plan had not been recognized and changed sooner.

Because of long latency periods, however, these will only help future patients, and not current ones. Therefore, well-coordinated quality management that minimizes known risks in the process is necessary as a second pillar. This is especially significant because individual radiation treatment consists of a chain of very complex individual steps that are conducted by different specialized groups and parties with complementary expertise (Fig. 15.2).

Over the years, this experience has set in motion an intensive discussion as well as quality assurance and/or process quality improvement measures.

Decisive steps included:

- Evidence-based guidelines for determining a therapeutic corridor;
- The individual radiation therapist’s obligation to provide follow-up care in order to monitor both effects and side effects on his own patients.
- The obligation to set up an internal departmental reporting system to recognize errors and critical events, including rules for external reporting (CIRS).
- Setting up external audits at regular intervals (medical sites as per Section 83 StrSchV [Strahlenschutzverordnung, Radiation Protection Ordinance]) that monitor the medicophysical and medical quality of radiation treatment on site and make suggestions for improvement.



Strahlentherapeutische Kette adaptiert n. W. Schlegel (DKFZ)	Radiation therapy chain adapted from W. Schlegel (DKFZ)
Präzisionsstrahlentherapie	Precision radiation therapy
Immobilisierung	Immobilization
Tumorlokalisation	Tumor localization
Patientenrepositionierung	Patient repositioning
Therapie	Therapy
Qualitätssicherung und Verifikation	Quality assurance and verification
Bildgebung	Imaging
evtl. 4-D Bildgebung	Possibly 4D imaging
Fusionsbildgebung Funktionelle Bildgebung	Fusion imaging Functional imaging
Therapieplanung	Therapy planning
Inverse Planung Adaptive Planung	Inverse planning Adaptive planning
Geringe Interventionsschwelle	Low intervention threshold
Individuelle Dosimetrie Volumenbildgebung Verschärfte Konstanzprüfung	Individual dosimetry Volume imaging Intensified consistency testing

Fig. 15.2 Individual radiation treatment consisting of a chain of very complex individual steps, Bille and Schlegel (1999); for translation of the German expressions, see table given in figure

Summary

The description and quantification of risks of radiation medicine and analysis thereof require observation over very long periods of time and integration of complex data. This goes above and beyond the capacities of individual treatment providers and even large institutions.

Meaningful risk management means that suitable instruments for measuring the quality of results must be continuously developed and utilized more rigorously. Differences with respect to pharmaceutical research must be realized and accepted.

Only in this way can technological progress in radiation medicine be translated into real treatment in an adequately safe and speedy fashion.

The expansion of regional and national cancer registries can achieve part of the documentation of long-term effects and their evaluation. However, this will only be successful if the willingness to interlink with other databases (e.g. morbidity data from health insurance companies) increases.

However, general registries are not capable of answering special questions (e.g. new technologies, changed dosage plans, medication interactions, etc.) quickly, since additional parameters not originally foreseen in the registry database must usually be recorded for this purpose. In order to estimate the actual extent of effects, prospective recording in the context of dedicated care research is necessary.

For both approaches, cross-sector expertise (IT and big data mining, epidemiology and care research, data protection and radio-oncology) is necessary and should be brought together in a dedicated consortium in a dialogue among treatment providers, patients, cost-bearers and health policymakers.

For established processes, it will be decisive to have procedures that ensure the best treatment for individual patients by recording and reviewing the process quality of the "radiation therapy chain." This must be recognized as an integral part of radiation treatment.

References

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