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Report from SSM's scientific council on ionizing radiation within oncology, 2011

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SSM perspective

Background

In 2009, the Swedish Radiation Safety Authority (Strålsäkerhetsmyndigheten, SSM) appointed a scientific council on ionizing radiation within oncology. The council consists of scientific experts in the fields of oncology, radiobiology and medical physics. Their task is to annually review and evaluate scientific developments in radiotherapy and to give SSM advice in issues where a scientific examination of different views is necessary. The council began its work in the autumn of 2009 and this is the second report presented.

Objectives

The scientific council is obliged to produce an annual report on radiotherapy issues. The report will summarize recent scientific knowledge.

Results

Many cancer patients are treated in accordance with written guidelines or clinical trial protocols. The scientific council states that the radiotherapy part in those guidelines and protocols is less well specified than other therapies such as surgery and chemotherapy. This report identifies the key aspects of modern radiotherapy from international radiotherapy organisations and scientific papers in order to develop written radiotherapy guidelines and clinical trial protocols.

Associated relevant information to be listed in protocol templates are analyzed and discussed. The report provides a framework for the description of the entire radiotherapy process in both clinical care programmes and trial protocols based on clinical as well as physical aspects. The framework includes preparatory imaging, specification of treatment prescription, relations to other therapies and treatment planning. The results are applicable in protocols for palliative care as well as for advanced treatments.

The report discusses the importance of clinical evaluation in clinical trials and in routine care as well as the importance to follow quality management guidelines when writing protocols and treatment programmes. Finally the report also discusses special considerations for brachy therapy. The scientific council recommends SSM to promote the development of protocol templates to use when writing the radiotherapy part in care programmes and clinical trial protocols.

Project information

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This report concerns a study which has been conducted for the Swedish Radiation Safety Authority, SSM. The conclusions and viewpoints presented in the report are those of the author/authors and do not necessarily coincide with those of the SSM.

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Content

1. Introduction

Advances in many aspects of diagnosis, staging and treatment have resulted in improved results with more patients living disease-free for long time periods.
Technical and computer improvements have facilitated this development in imaging, surgery and radiotherapy. At the same time new drugs with activity in at least sub-populations of many cancers have been developed. Combinations of treatments are used for more and more patients since these have shown superiority in clinical trials. The evidence-base is continuously increasing.

The development has improved outcome but also increased complexity. The demands on written guidelines describing all relevant steps in the radiotherapy process therefore increase. In order to keep up with the increasing knowledge base and to secure high and equal quality for patients wherever they live, it has been realised that the guidelines must be (at least) national, although regional or local adaptations can be required. In Sweden, the six Regional Cancer Centres (RCCs) have the duty to co-ordinate this work. Regional or national guidelines (Care Programmes) have existed since decades, but have increased in numbers substantially during the past few years. The number of national quality registries has increased in parallel. These allow evaluations of the quality of the interventions described in the Care Programmes but are also a rich source for outcome research (1). Clinical trial protocols have sometimes also been integrated into the Care Programmes, although most of them are kept separate.

Today many cancer patients are thus treated in accordance with written guidelines or clinical trial protocols. However, in combined treatment regimens, it is common that the radiotherapy part is less well specified than other therapies. Several very important parts of the radiotherapy process are not sufficiently well dealt with and thus open for local variations. A well-specified study protocol/clinical guideline is important, as it is fundamental for the evaluation of the outcomes, including patient-reported outcomes such as quality of life, and hence the development of future radiotherapy. It is known that protocol adherence is associated to better outcome in several malignancies (2-5).

Well-specified treatment guidelines are important from a radiation protection point of view. Suboptimal radiotherapy routines may not only decrease the probabilities of tumour control but also increase the absorbed dose burden for the treated patients. Well-defined treatment protocols facilitate optimisation and evaluation of treatment planning and may therefore shorten the radiotherapy process, besides improv-

ing safety. Therefore, SSM's scientific council has decided to focus on the writing of guidelines in this year's report, to be applicable both for clinical guidelines/care programmes and for trial protocols. To our knowledge, there are no general guidelines for how to describe modern advanced radiotherapy in protocols. The latest report on this topic was until recently the European Organisation for Research and Treatment of Cancer (EORTC) guidelines published by Bolla et al. more than 15 years ago (6), and, although it was detailed and has been useful for conventional radiotherapy, it is not fully applicable for modern techniques. The Radiation Oncology Group within EORTC realised this and recently published an update of guidelines on how to write clinical trial protocols involving advanced radiation therapy techniques (7).

The members of the scientific council on ionising radiation within oncology producing this report were as follows:

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2. Development of radiotherapy and review of current guidelines

The continuous and fast advancements in radiation therapy and imaging technology, together with a growing body of knowledge and evidence in the field of clinical radiobiology, are constantly changing the radiotherapy world. Several new diagnostic modalities are available, and a whole new area has emerged related to image registration. New hybrid imaging modalities for target definition, new devices able to combine advanced imaging techniques and dose delivery have been developed. New questions regarding the management of heterogeneous and moving targets have received increasing attention. New recommendations from the International Commission on Radiation Units and Measurements (ICRU) have been issued for prescribing and reporting intensity modulated radiotherapy (8).

Perhaps the most dramatic change, however, lies in the introduction of inverse treatment planning. This requires that treatment objective and constraints are specified and prioritised with more care and in greater detail than before. For the realisation of inverse optimised treatment plans, many new delivery modalities such as intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT) and tomotherapy are available. Some of the novel beams have unconventional spectral characteristics, and there are other new dose computation and optimisation issues as well, that need to be specified in more detail in modern radiotherapy protocols. Due to the complicated dose- and volume prescription required for an inverse optimised treatment plan, also the plan evaluation procedure must be revised accordingly. Different priority orders and objective weighting factors may need to be evaluated in parallel by specially devised procedures. Possibilities to invoke radiobiological models for tumour control and normal tissue complication probabilities are also developed. A new area is also image-guided radiotherapy (IGRT). This brings along many variables that require specification in order to ensure the desired level of precision throughout the course of the treatment. Finally, the substantially increased complexity of the radiotherapy implies that aspects on quality assurance (QA) require significant updates.

Changes come also from other fields; independently of the technological development, a paradigm shift was introduced about twenty years ago in radiation oncology by the so-called stereotactic radiotherapy (9, 10). This brought new knowledge about tumour and normal tissue response when treating with extreme hypofractionated treatment schedules. This has strongly affected treatment choices in several diagnoses (9-12). As a result of this technical solution, an increasing number of hypofractionation treatment protocols are nowadays applied in routine clinical practice and in clinical trials. The develop-

ment is also supported by new data about radiation and fractionation sensitivity of tumour cells, which helps to tailor fractionation protocols according to specific parameters (13, 14). Inhomogeneous dose prescription to the target has become a general concept, to be obtained during one treatment course or as a result of the combination with a boost. Furthermore, combined modalities, e.g. external radiation therapy and brachytherapy, are also getting increased interest.

In some cases, radiotherapy protocols for specific pathologies are accessible via the internet, e.g. the Cancer institute NSW, Australia (https://www.eviq.org.au/); most of them, however, are prepared according to local features. At another level societies and organisations are acting to adapt general radiation therapy guidelines to the new era. This is more a necessity than a need; when the present intention of most centres is to increase patient accruals in trials the harmonisation among both methods and contents of prescription and reporting is a condition for realising this. The work of framing the description of radiation therapy in general programmes, regional, national or international, is as usual a major challenge. Although not a general guideline, a prescription template for protocols from the Radiation Therapy Oncology Group (RTOG) is available at their website (http://www.rtog.org). This document focuses on dose prescription aspects, and includes a discussion on the balance between dose prescription requirements and patient accrual.

The only general guidelines that we know of are those of the EORTC. The first EORTC guidelines from 1995 are divided into several sections describing the radiotherapy process in subsequent steps, including preparation (positioning of the patient, patient data acquisition, and volumes of interest), treatment planning (treatment technique, normal tissue sparing, dose computation, and dose specification), simulation (simulation procedure), and delivery (equipment, treatment verification) (6). A separate section on brachytherapy is also included, as well as a chapter on QA. The EORTC guidelines follow the treatment preparation procedure and the treatment process, which makes it still useful for conventional radiotherapy. For modern advanced radiotherapy, however, it needs to be updated. Since this report was written, significant changes have been introduced in many links of the radiotherapy chain as briefly outlined above. EORTC has, in parallel to the development of our report, also recognised the lack of modern guidelines and their second report (7) was published at the time of completion of our report. They mostly focus on the description of clinical trial protocols involving advanced radiation techniques and then mainly discuss the clinical aspects in the trial protocols. Implementation of QA procedures for advanced radiotherapy is also briefly described.

3. Aim of the present report

The purpose of this report is to identify important aspects of modern radiotherapy in order to assist in writing of radiotherapy protocols and clinical guidelines. The modern radiotherapy process and relevant issues to be listed in protocol templates are analysed and discussed. This report provides support and is applicable in the writing of protocols for both simple treatments used, e.g. in palliative situations, to advanced treatments where the highest requirements should be used or tested.

4. Analysis of the modern radiotherapy process with suggestions for new guidelines

This section describes the modern radiotherapy process in a way suitable for writing the radiotherapy part in guidelines/clinical trial protocols. The radiotherapy process is analysed, relevant issues are addressed, and in some cases the implementation of new approaches are suggested.

Factors that must be established before the patient is referred to the radiotherapy department (e.g. patient prognostic factors such as age, co-morbidities, performance status; tumour prognostic factors such as differentiation, molecular characteristics, staging; and treatment intention) have generally been addressed at multi-disciplinary conferences, and will not be discussed further. The choice of proper diagnostic tools for determining these factors is also not within the scope of this presentation. However, the entire radiotherapy process is based on these pre-therapeutic decisions, and it is essential that consistency is preserved through all following steps. Procedures for preparatory imaging, treatment planning, delivery and evaluation must all be designed in alignment with the intentions.

4.1. Preparatory imaging

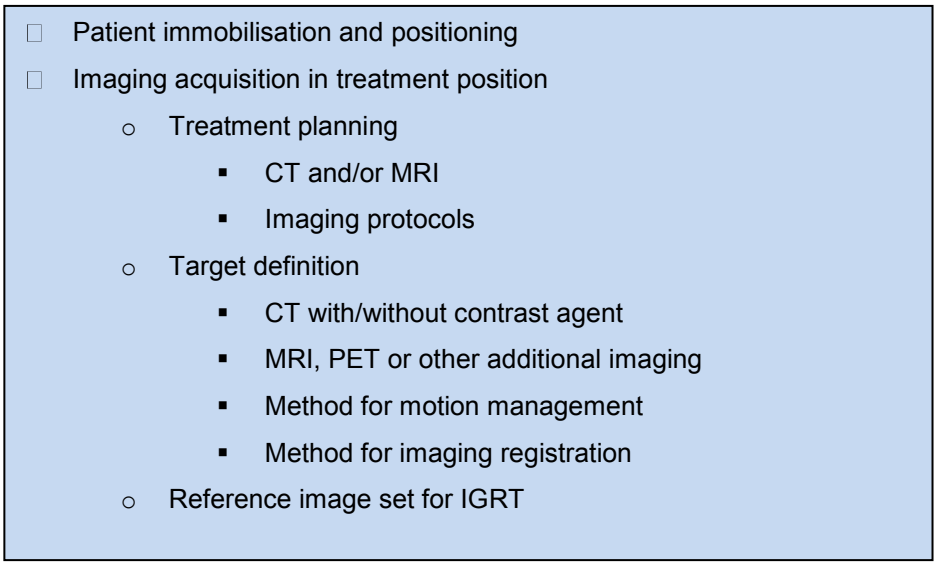
The preparatory process is aimed to provide the basis for target definition, treatment planning and image guidance procedures during the course of the treatment. In order to support co-registration of data from different imaging modalities, and to provide a rigid frame for image guidance, it is essential for all procedures that the patient immobilisation and positioning are well defined. Target definitions are generally performed on a computer tomography (CT) data set, with or without contrast agents, and supplemented with patient-specific clinical information. This data set is generally also the foundation for the

absorbed dose calculations performed in the treatment planning system. Since imaging parameters may have great influence on both volume delineation and absorbed dose calculations, it is important that all such information is properly chosen and specified.

In case additional imaging (e.g. magnetic resonance imaging (MRI) or positron emission tomography (PET)) is required, careful attention should be given to co-registration procedures, in particular if the data originates from separate machines (15-17). Rigid or deformable registration procedures may have different requirements (18, 19).

In cases where motion needs to be taken into account, time-dependent data (4D) are crucial (20, 21). The proper method of 4D imaging depends on the intended type of treatment delivery motion management (22-25). In its simplest form, the 4D data set can be used to apply necessary margin expansion to the target volume(s) and organs at risk. More advanced forms of motion management include gating and tracking, which require time resolved image data sets (26-29). It is important to realise that the achievable margins are strictly related to the type and the frequency of the treatment verification procedure (see Ch 4.6).

Figure 1. Summary of preparatory imaging



4.2. Specification of treatment prescription

A specific statement of a radiation treatment objective includes information on both geometry (volume specification) and dosimetry (absorbed dose prescription).

Volume specifications and absorbed dose prescriptions should be specified in accordance with the recommendations by the ICRU (8, 30-32). It should be stated how the gross tumour volume (GTV) and organ-at-risk volumes (OAR) are delineated, and which diagnostic tools are used. The delineation in three-dimensions of normal tissues is often affected by large inter-observers variability. This is also due to indistinctness of instructions, beyond the lack of an adequate imaging platform, as also the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) review (33) has underlined. In order to decrease this variability and to promote consistency in normal tissue delineation among observers and among centres several atlases have been prepared (34, 35).

If the GTV is considered as composed of several sub-volumes, this should be stated specifically. For the clinical target volume (CTV) and internal target volume (ITV), instructions for the delineation should be included. It is important to state the grey scale window settings to be used when defining the different target volumes. The planning target volume (PTV) and planning organ-at-risk volumes (PRV) are assumed to account also for motion related uncertainties, most commonly by applying an uncertainty margin to the CTV, determining the PTV (and similar for the PRV). The margins applied depend on equipment and patient immobilisation, and should be stated. The size of the margin can be based on direct or indirect observations of target motion in real patients, and statistical models have been developed for use in clinical practice (36).

The naming of target and OAR volumes should be specified in the protocol. Suggestion for a standardised naming convention for use in radiation therapy was recently proposed by a number of international radiotherapy societies (37).

There are alternative possibilities to account for motion related uncertainties. One way is to include the spatial distribution into the treatment planning calculations by convolving the dose calculation with a motion function, with the result that larger fields are required (38). In any case, the additional margin for motion uncertainties leads to larger irradiated volumes, and potentially an increased risk for unwanted effects on surrounding tissues. In the case of breathing motions, the required margins become particularly large, and as a consequence, other alternatives have been developed (23).For instance, the patient can be asked to hold breath during the time of irradiation (39). Active

breath-hold techniques are designed to support the patient not to breathe for prolonged times (40). Another alternative, which is more comfortable for the patient, is to gate the irradiation for certain parts of the respiratory cycle in order to minimise the influence of the motion during the time of irradiation (41). This approach also has the advantage that the irradiation window can be chosen for a phase in the respiratory cycle when the target is in a favourable position relative to nearby risk organs (42). The most advanced alternative for motion management is to use tumour tracking. This can be realised by using a linac mounted on a robotic arm (43), or, on a conventional treatment unite by utilising the multileaf collimator dynamically to conform to the target motion in real time (44, 45). This method has the advantage of both higher delivery efficiency and less residual target motion than the breath-hold and gating techniques.

As mentioned above, a complete prescription includes both volume and dose specifications, preferably in terms of composite dose-volume objectives for each structure. The situation is further complicated by the fact that the two main objectives of radiotherapy, i.e. to treat the target tissue and to spare the healthy tissue, are always mutually conflicting. Therefore, the relative importance of these two objectives must be stated explicitly in the treatment prescription. If this is not the case, the same prescription would not be able to discriminate between, on the one hand, a plan that emphasises good target coverage at the expense of somewhat higher doses to the risk organs, and on the other hand, a plan that emphasises a low dose to the risk organs at the expense of less target coverage (within clinically acceptable limits). Indeed, there is often more than one organ of interest, and sometimes there are also differentiated target volumes. In such cases, the trade-off between the different treatment objectives will have multiple dimensions, which makes it even more challenging to pin down a well-specified treatment prescription (the American Association of Physicists in Medicine (AAPM) Summer School 2011). Generally speaking, a complete IMRT treatment prescription will require specified objectives for close to every region exposed to the treatment. The reason is that any region that is not explicitly constrained may be used freely by the optimiser, in which case unexpected results may occur (46)**.** Two plans may look nearly equivalent, except perhaps for a hotspot that may have occurred outside any constrained region of interest, and which could easily be overlooked in the treatment plan evaluation.

One possible way to address this issue may be to device criteria describing what to prioritize when producing, evaluating and comparing plans. This could mean, for example, having CTV coverage as a primary priority, then to uphold dose restrictions to critical organs as a secondary priority, then PTV coverage as a third, dose to non-critical

OARs as a fourth, and finally dose conformity. An example of such a prescription priority is presented in Table 1. These absorbed dose objectives and constraints could be based on published guidelines e.g. QUANTEC data (47).

Table 1. Example of dose prescription

Priority	Volume	Endpoint for normal tissue	Objective or constraint
1	CTV		D_{min} ≥ 95%, Dmin≥ 74 Gy
2	PTV		$V_{95\%}$ ≥ 95% V_{74Gy} ≥ 95%
3	Rectum	Bleeding gr 2	$V_{90\%}$ ≤ 15% V_{70Gy} ≤ 15%
4	PTV		$D_{99\%}$ ≥ 90% $D_{99\%}$ ≥ 70 Gy
5	Rectum	Bleeding gr 2	V75% ≤ 35% V59Gy ≤ 35%
6	Femoral heads	Fracture	D_{max} ≤ 70% Dmax≤ 55 Gy
7	Rectum		V65% ≤ 45% V51Gy ≤ 45%
8	Body		D_{max} ≤ 105% Dmax≤ 82 Gy

Dose prescription for a prostate cancer case. Observe that this is not a specific recommendation but an example of a dose prescription with prioritised objectives.

An emerging alternative is to prescribe a radiation treatment in terms of radiobiological effect parameters, such as a minimal required tumour control probability (TCP) and maximum tolerable normal tissue complication probabilities (NTCPs) for the exposed healthy organs (48). The risk for treatment-induced cancer is also an important side effect of radiotherapy that may be specified in the prescription of a radiation treatment in the future (49).

Finally, the temporal aspects of the treatment delivery, i.e. time and fractionation scheme is an important part of the radiotherapy prescription, in particular if unconventional fractionation schemes are used, e.g. two fractions per day. In this case it is important to specify the minimum required time between the two fractions to allow for an as complete as possible repair, e.g. at least 7h (50, 51). Note that the constraints used for conventional fractionation should not be applied to other fractionation schedules without considering correction for fractionation effects (47, 52).

The importance of keeping the total treatment time and its influence on tumor control has been described by several authors (53-56). There should therefore be a plan for the management of unintended interruptions (57). Well-described examples are available by Dale et al. 2002 and Jones et al. 2007 (58, 59).

Figure 2. Summary of specification of treatment prescription (volume and dose)

- Volume specifications
  - ICRU recommendations (GTV, CTV, ITV, PTV, OAR)
  - Definitions of treatment volumes including OAR
  - Standardised naming of treatment volumes
  - Motion management
    - Margins
    - Tracking, gating
- Absorbed dose prescription
  - Dose prescription reference (point or volume)
  - Dose-volume objectives and constraints
  - Models for biological optimisation objectives
  - Prioritised dose-volume objectives and constraints
- Time and fractionation
  - Dose per fraction
  - Number of fractions per day
  - Number of treatment days per week
  - Total number of fractions
  - Total dose
  - Time between fractions if multiple per day
  - Boost (sequential, concomitant or simultaneous)
  - Maximum allowed overall treatment time
  - Management of unintended interruptions

4.3. Relation to other therapies

Radiotherapy is one of several modalities used in the management of most cancers, in which case the relevant timing in relation to surgery and/or chemotherapy (or other drugs) and potential interactions between the therapy modalities must be stated.

Surgery is often part of the cancer therapy. Radiotherapy may then be used preoperatively to allow surgery (down-sizing or down-staging) or minimise the risk of recurrence (neo-adjuvant) or postoperatively to minimise the risk of loco-regional recurrence (adjuvant). Occasionally, intraoperative therapy is used. In the case of preoperative radiotherapy, the treatment intention should be stated, i.e. neo-adjuvant treatment, down-staging or downsizing (60). Since it is important to keep the times between the radiation treatment and surgery, whether given pre- or postoperatively, time limits should be properly defined. Preoperatively there may be specific time windows to minimise toxicity and prevent tumour repopulation and good co-operation between the different involved departments is required. Allowing too little time after surgery makes wound healing difficult, and on the other hand, too protracted time gaps will increase the probability of tumour recurrence.

If concomitant chemotherapy or other drugs are given the timing of the radiation treatments and the drug administration should be carefully stated. When using drugs in combination with radiotherapy unexpected toxicity may occur. In the evolution of new drugs, especially targeted therapies, little is known of combinatory effects. Special care must thus be considered when using known constraints for normal tissues, when combining radiotherapy and drugs (33, 49, 61, 62).

Reporting of late effects are scarce, and in particular when radiotherapy and drugs are combined (33, 49). It is preferable that the protocol includes reporting of late damage with prolonged follow-up of the patients. Better routines how to facilitate long-term follow-up, also outside trial protocols, are of great importance to increase knowledge about late effects from combined treatments, and should be developed.

Figure 3. Combined treatments

- Surgery
  - State if radiotherapy is planned pre- or post-operatively
  - If preoperatively, state the purpose
  - Timing requirements between surgery and radiotherapy
- Drug therapy
  - State if radiotherapy is planned pre-, concomitant to, or post chemotherapy
  - Reference to chemotherapy protocol
  - Timing of chemotherapy in relation to the course and fractionation of the radiotherapy

4.4. Treatment planning

Treatment planning is a central part of the radiotherapy process and needs to be clearly specified in clinical guidelines and study protocols. The process may be subdivided in discretion of treatment technique and equipment, dose computation and treatment plan optimisation and evaluation.

4.4.1. Treatment technique and equipment

If the treatment objectives are complete and well specified, the choice of treatment technique and equipment is subordinated. However, due to the vastly different treatment techniques available today, it may in some situations be desirable to specify allowed alternatives.

4.4.2. Dose computation

It is important to ensure and uphold traceability to international dosimetry standards. This is generally achieved by following international reference dosimetry protocols, e.g. the International Atomic Energy Agency (IAEA) TRS-398 (63). Participation in dosimetry audits are highly recommended in order to ensure high quality (64-66). The dose computation model in the treatment planning system may have limitations, regarding for instance heterogeneity correction models. It is mandatory to specify the type of dose computation algorithm (67) etc., and to be aware of its applicability in clinically relevant ge-

ometries (64, 67-72). Preferably calculation uncertainties should be estimated (23).

Guidelines should include requirements on the size and spatial resolution of the dose matrix, since the evaluation of dose volume histograms (DVH) and DVH-parameters may be greatly distorted if the dose matrix is not adequately adjusted to the dose gradients and the size of the smallest volumes of interest.

4.4.3. Treatment plan optimisation and evaluation

In principle, a rigorous evaluation of a treatment plan would require a thorough review of the dose distribution in full 3D, *i.e.* in all the available 2D sections. However, this is not practical. Instead, the information of the dose distribution is generally condensed into voxel statistics (DVH) without providing spatial information (73). In the interest of having a single quantitative measure of the objective, DVHs information are often further condensed into percentiles (such as D_{vol} or V_{dose}), arithmetic means, generalised means, e.g. equivalent uniform dose (EUD)**.**This reduction may be necessary in order to obtain manageable quantitative measures, but one should be aware of the fact that, potentially critical information may be lost in the process. Objectives expressed in terms of radiobiological models are likely to be used clinically more often in the future, but the same principles should apply. However, it is important to note that in order to measure the actual degree of objective fulfilment, the treatment plan should be evaluated in terms of the same parameters used in the prescription. An NTCP evaluation is therefore only relevant if also the prescription is stated in terms of NTCP.

As discussed in section 4.2 above, inverse treatment planning requires that the constraints and optimisation objectives are prescribed in great detail and that their relative importance is specified accordingly (Table 1). In practice this is a matter of determining the proper weighting factors for the optimisation algorithm. Given that there are multiple constraints and optimisation objectives, the optimisation algorithm can only produce so called Pareto-optimal results (74-76). A Pareto-optimal solution is optimal for a specific set of weighting factors, whereas another set of weighting factors gives another Pareto-optimal result. One objective may then be improved, although it will be at the expense of another. In order to obtain a treatment plan fulfilling the intentions, it is advisable to systematically vary the involved weighting factors. This approach allows the whole trade-off between the prescribed objectives to be considered when selecting the final treatment plan.

Figure 4: Summary of treatment plan optimisation

- Treatment technique and equipment
  - Radiation type, beam quality and dose rate
  - Irradiation geometry
- Dose computation
  - Reference dosimetry according to international standards
  - Participation in dosimetry audit program
  - Dose calculation algorithm, grid size and resolution
- Optimisation
  - Definition of help structures
  - Machine dependent constraints
- Treatment plan evaluation
  - Variation of weighting factors, choice of pareto-optimal plans

4.5. Special considerations for brachytherapy

Brachytherapy (BT) is increasingly being used in modern curative treatment of cancer. It can be applied either as monotherapy or as a boost to part of a larger volume treated with external beam therapy. BT can be used as an after-loading technique with high dose-rate (HDR), low dose-rate (LDR) or pulsed dose-rate (PDR) mode. The technique can also be used as a permanent implant. BT is a multifaceted technique, where clinicians and physicists have developed recommendations and guidelines for each and one of the different tumor/organ areas. Examples are for prostate cancer (77-80), gynecological malignancies (81-87), breast (88), and head and neck cancers (89).

BT requires a multimodal team work where oncologists, radiotherapists, medical physicists, anesthesiologists and dedicated radiotherapy nurses are actively involved. It is also important to involve diagnostic radiologists and the modern radiological imaging techniques for delineation of tumor extension.

Similar types of anatomy-based algorithms as the ones used for dose calculation in external beam radiotherapy are now being increasingly applied in BT. The treatment planning systems are based on modern imaging techniques such as ultrasound, MRI and CT. The dose planning can be performed prior to therapy, thus giving information on the precise placement of applicators/needles in the tumor/organ. On-line dosage planning has, with the advent of even faster dose planning sys-

tems, been more frequently used during the last years in treatment of malignancies such as e.g. prostate cancer. This has streamlined the process and at the same time reduced the risk of repeating the pre-planning procedure due to unforeseen anatomic obstacles such as interfering parts of the skeleton or adjacent organs. It is important that the physician in charge assures before start of treatment that the dose prescribed to the planning target volume is obtained and that dose constraints in organs at risk are kept.

Over the years, separate guidelines have, as mentioned above, been developed for various tumor diagnoses. These guidelines have all formed a major step forward in defining how and when to use the different BT techniques described above. The majority of the guidelines focus on practical aspects related to a specific tumour diagnosis. These also include important aspects on topics such as radiation protection, quality assurance and education. Still, there is a need, as in external beam radiotherapy, for further development of guidelines how to write protocols for clinical trials of BT. Such work is currently ongoing.

4.6. Clinical evaluation

In clinical radiotherapy assessment of acute and late toxicity and efficacy is essential to evaluate the treatment to improve outcome for future patients. To define criteria for radiotherapy follow-up is important not only in clinical trials but also in routine care.

During the course of the treatment acute side effects should be monitored and adequate actions taken. This is routine at all radiotherapy departments and may result in treatment modifications. In chemotherapy, dose modification after monitoring and grading of acute toxicity is routine and well described in protocols since decades. This approach may be of relevance also in dose-intense radiotherapy, in particular when combined with drugs and requires the use of pre-defined toxicity assessment scales such as common terminology criteria for adverse events (CT-CAE), EORTC/RTOG.

In adaptive radiotherapy the treatment is adjusted during the course according to tumour response or toxicity in order to maximise tumour control and/or minimise toxicity in the individual patient (90).For this approach a more extensive monitoring than presently used is required during treatment. Early assessment (within days or a few weeks after treatment start) of response in order to change treatment schedule or modality during the radiotherapy course is one example of adaptive radiotherapy. This requires specifications of early response assessment modality and timing of the assessment. Presently much research is devoted to repeated PET or MRI imaging during therapy. Actions tak-

en to insufficient response could be modified radiotherapy (increased dose, changed fractionation or modified target volume) or a change of treatment modality (like surgery rather than radio-chemotherapy, as presently explored in oesophageal cancer).

Follow-up of tumour response is essential for evaluation of radiotherapy. It should be stated in the protocol the timing between the end of therapy and first evaluation as well as the timing of subsequent evaluations. It is also important to state the method for evaluation, e.g. MRI, CT, PET-scan, clinical evaluation with biopsy and pathological assessment depending on the disease in addition to the intention of the radiotherapy. Response criteria should follow international recommendations and disease progression should be recorded as local, regional or distant progression. In radiotherapy local control is in most cases a much better outcome measure than grading of response according to tumour shrinkage as assessed by imaging. Quality of life, if considered to be of relevance, should be assessed at pre-defined timepoints using validated questionnaires. In case of reporting to quality registries, the actually given therapy should be reported, which sometimes deviates from the originally intended therapy.

Recording of late toxicity is essential in radiotherapy but is often neglected due to lack of formal follow-up schedules in everyday practice. Appropriate assessment of late toxicity is seldom done in clinical trials due to the long follow-up times needed. As previously stressed (49) this is particularly important using new radiotherapy techniques such as IMRT alone or in combinations with drugs. The reporting of late toxicity should therefore be included in future quality registries where radiotherapy is a treatment option. A fundamental requirement for description of late toxicity is an adequate description of given radiotherapy and a systematic follow-up of patients. Follow-up of late toxicity in clinical trials may require a more detailed description of late toxicity with special consideration to OAR function. In such cases a description of assessment method and timing of evaluation is necessary.

In Sweden there is today no central registry for reporting serious unexpected adverse events of radiotherapy. To improve safety this should be initiated by the regulatory authorities. Reporting to such a registry should be mandatory as is the case for drug side effects (49). In order to increase the likelihood of early detection of potential mistreatment, it is strongly advisable to be observant to any complaints patients may have during or after the treatment session (91). All incidents and accidents should be reported via established local and/or national systems.

4.7. Quality management

Existing quality management guidelines should be followed when writing radiotherapy study protocols and treatment programmes. General quality management tools, in addition to process mapping and risk analysis (92), contain parts that should be specified in care programmes and study protocols.
This includes dummy run procedures that are performed before the start of a new radiotherapy study, or the commissioning of a new treatment modality. Dummy runs can also be performed during ongoing trials in order to check and further improve the protocol compliance.

A pretreatment dummy run should be performed when a new trial/care program is initiated. The main purposes of the dummy runs are to assure compliance to the study and to find any ambiguities in the guidelines. The dummy run often consists of two parts, i.e. segmentation of structures (targets and organs at risk) and treatment planning (93-97).

For dosimetry (measurements and independent calculations) and IGRT procedures (on-line and off-line), both pre- and during treatment, a strategy has to be defined to identify and act about the correction of the systematic deviation as compared to the treatment plan. This means, for instance, that acceptance criteria for the evaluation should be stated. The additional absorbed dose contribution due to IGRT procedures shall be estimated (49). For international guidelines, reports and other related documents, see e.g.:

- AAPM reports at:
  http://www.aapm.org/pubs/reports/
- American Society for Radiation Oncology (ASTRO) reports at:
  https://www.astro.org/ ClinicalPractice/Guidelines/Index.aspx
- European Society for Radiotherapy & Oncology (ESTRO) guidelines at:
  http://www.estroeducation.org/publications/Pages/ESTROPhysicsBooklets.aspx
- IAEA documents at:
  https://rpop.iaea.org/RPOP/RPoP/Content/InformationFor/HealthProfessionals/2_Radiotherapy/index.htm

Figure 5. Summary of quality control

- Preparatory
  - Dummy run
- Pre-treatment patient specific dosimetry
  - Independent calculations, measurements, etc.
  - Analysis and action levels
- In-vivo dosimetry
  - Methods, frequency
  - Analysis and action levels
- IGRT procedures
  - Imaging type and frequency
  - Analysis and action levels
  - Statement of extra absorbed dose contribution

5. Conclusions

New guidelines for writing protocols for modern radiotherapy are required. The scientific council suggests that SSM promotes the development of protocol templates to be used when writing the radiotherapy part in care programmes and clinical trial protocols. The recently published EORTC guidelines mainly focus on the clinical aspects of clinical trial protocols. In the present report our intention has been to provide a detailed framework for the entire radiotherapy process including clinical as well as physical aspects for the description of the radiotherapy process in both clinical care programmes and trial protocols.

6. References

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The Authority reports to the Ministry of the Environment and has around 270 employees with competencies in the fields of engineering, natural and behavioural sciences, law, economics and communications. We have received quality, environmental and working environment certification.

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