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ORIGINAL ARTICLE

A template for writing radiotherapy protocols

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ABSTRACT

Background. Well-specified and unambiguous treatment protocols are essential both for current practice and for the future development of radiation therapy. In order to provide assistance for writing good protocols, irrespective of treatment intention and complexity, up-to-date guidelines are highly desirable.

Methods. We have analysed the radiotherapy work-flow, including clinical and physical aspects, such as preparatory imaging, treatment planning, delivery and evaluation, with the aim to outline a consistent framework covering the entire radiotherapy process.

Results. Based on the analysis, a recipe-style template for specifying the description of the radiotherapy process has been designed. The template is written in a general format, which allows for modified phrasing, and should be customised for the specific clinical situation and diagnosis, as well as facility resources.

Conclusions. The template can be used as a tool to ensure a consistent and comprehensive description of the radiotherapy section of clinical guidelines, care programmes and clinical trial protocols.

In radiotherapy, adherence to study protocols is important for the evaluation of the treatment outcome, both regarding tumour response and normal tissue complications, and patient-reported outcome, such as quality of life. Furthermore, it has been shown that protocol compliance is associated to better outcome in several malignancies [1,2]. Well-specified and unambiguous protocols are therefore essential both for current practice and its future development. However, it is common that the radiotherapy process is not always sufficiently dealt with, e.g. in combined treatment regimen protocols with chemotherapy. This opens for local variations, and radiotherapy process-oriented guidelines for writing study protocols are therefore highly desirable in order to reduce such uncertainties and to improve adherence.

The European Organisation for Research and Treatment of Cancer Radiation Oncology Group (EORTC ROG) has recently published new recommendations for writing protocols for multicentre clinical trials, including an extensive description of the quality assurance (QA) programme for EORTC trials [3]. In particular, the radiotherapy part of this document is an update of the corresponding part of the previous EORTC recommendations from 1995 [4], focusing on the requirements of advanced external beam delivery techniques in multicentre clinical trials.

In the recent work within the Swedish Radiation Safety Agency's (SSM) Scientific Council on Ionizing

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Radiation within Oncology, we analysed the contemporary radiotherapy process and made suggestions for new protocol guidelines applicable both for study protocols and care programmes, irrespective of treatment intention and complexity [5]. Based on this report, we proposed a template-styled master protocol [6]. A preliminary version of this template has been used in Sweden, and found to be very practical.

Based on this experience, we believe that a template-styled master protocol can be very useful, and the aim of this work was to present an improved template also considering the structure of the recent EORTC recommendations.

The template

The proposed template is presented in Table I. The template was produced based on an analysis of the contemporary radiotherapy process, with the focus set on procedural aspects [3,5]. It is written in a general format and should be completed and customised for the specific clinical situation and diagnosis, as well as facility resources. It should be incorporated into another document where all other relevant information should be detailed (e.g. inclusion and exclusion criteria in case of a trial, timing and relation to non-concomitant treatments, follow-up of late effects, etc.). In order to facilitate the protocol writing, it has been our intention to format the template in full sentences, rather than as a bullet list. The texts within curly brackets are examples and shall be replaced appropriately. Square brackets shall be replaced with numerical values. Some items may need to be copied in case there are more than one relevant alternative. If needed, the protocol author may decide to add an option to leave a certain item to the protocol user's discretion. For instance, the CTV to PTV margin might be individually determined by the centre, depending on the department's equipment and routines, but should then be reported. Items that are not applicable to the particular protocol should be deleted, and the final phrasing of the body text is of course at the protocol author's preference.

Discussion

The scope of the template presented in this work is similar to chapter 2 of the recent EORTC recommendations [3]. Thus, the template is focused on the radiotherapy process itself, and factors that must be established before the patient is referred to the radiotherapy department are not included. Nevertheless, the entire radiotherapy process is based on these pre-therapeutic decisions, and it is essential that consistency is preserved through all following steps. As an example, procedures for preparatory imaging, treatment planning, delivery and evaluation must all be designed in alignment with the treatment intentions.

Within this scope, we have made an attempt to include some of the recent developments in personalised radiotherapy. While personalised medicine is generally associated with predictive biomarkers, the individualisation of radiotherapy treatments also builds on the development of imaging modalities and the evolution of highly conformal treatment techniques. Therefore, we have in this template included items regarding the use of MRI for dose calculations, biological treatment objectives, inverse treatment planning, and treatment adaption.

In particular we have highlighted the prioritisation of the treatment planning optimisation objectives. In our experience this issue is seldom dealt with properly. As this is of fundamental importance for an effective implementation and fulfilment of the prescription in the treatment planning optimisation, we recommend that criteria describing what to prioritise when producing, evaluating and comparing plans in the clinical situation are clearly defined a priori. An example of such a list of prescription priorities, taken from a clinical protocol for radiotherapy of head-and-neck cancer, is presented in Supplementary Table I (to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.981285). This is a useful tool for all kinds of diagnoses (see e.g. [7]), and if it is well-enough specified, it may provide sufficient basis for protocol-driven, multi-modality treatment planning optimisation [8]. We strongly recommend that a table like this is included in the radiotherapy protocol under planning aims and dose-volume constraints.

Furthermore, we have expanded the section on the treatment verification to also include treatment adaption. This template section contains items regarding geometrical adaption to changes in the patient's external or internal anatomy, as well as adaption to tumour and acute normal tissue response. Only the procedural consequences of acute toxicity during the course of the treatment, leading to modifications of the treatment, are included. It is recognised that issues regarding clinical evaluation during and post-treatment (e.g. acute and late toxicity, quality of life assessment, unexpected adverse events, and treatment efficacy) are essential to evaluate the treatment in order to improve outcome for future patients. To define criteria for radiotherapy follow-up, alone or in combination with other therapy, is important in routine care as well as in clinical trials. However, these aspects are not dealt with in the template, but should be specified in other parts of the study protocol/care programme.

Table I: External beam radiotherapy protocol template.

Facility and equipment

- The facility shall have equipment for {*IMRT; VMAT; gating; 4DCT; MRI; …*}.
- The make and version of the particular treatment equipment shall be reported.

Patient positioning and simulation

- Pre-treatment preparation
  - o A {*thermoplastic mask-mould; breast board; vacuum bag; leg fix; body fix; SBRT frame; SRT frame; …*} immobilisation device shall be {*manufactured; individualized; …*} for {*supine; prone; …*} patient position.
  - o {*Dental spacers; additional accessories; …*} shall be prepared and fitted to the patient.
  - o The patient reference coordinate system is defined by using {*tattoos; implanted fiducial markers; …*}, positioned [*d*] days before preparatory imaging.
  - o The patient shall have {*full bladder; empty rectum; …*} during imaging and treatment.
  - o For motion compensation, the patient is prepared by {*abdominal compression; respiratory training; …*}.
- Pre-treatment imaging
  - o For structure delineation, {*CT; MRI; PET; …*} imaging shall be performed with {*contrast; tracer; …*} according to {*scanning/acquisition protocol*}.
  - o The {*CT; MRI; …*} scanning shall cover {*anatomical landmarks*}.
  - o Slice-thickness and inter-slice gap shall be within [*x*] mm.
  - o Imaging for treatment planning dose calculations shall be performed with {*CT; MRI*} according to {*scanning/acquisition protocol*}. If applicable, any pre-processing of the imaging data (e.g. conversion to appropriate radiation interaction data) shall be reported.
  - o Time resolution shall be obtained by using {*4D imaging; prospective gating; …*}.
  - o Image sets from the different modalities shall be co-registered by using {*deformable; non-deformable; …*} registration technique.
  - o Reference imaging for IGRT shall be made with well-defined reference system based on {*internal fiducials; optical surface scanning; …*}.

Volume selection and definition

- The recommendations made by ICRU shall be followed.
- The naming of target and organs-at-risk volumes shall follow {*recommendations*}.
- The Gross Tumour Volume(s) (GTV) shall include {…} based on {*CT; MRI; CT-PET; US; …*}. Any boost GTV shall include {…}.
- The Clinical Target Volume(s) (CTV) shall include {*GTV plus x mm margin for microscopic extent of tumour; adjuvant lymph node stations; …*} based on {*clinical assessment; anatomical atlas; …*}.
- The Planning Target Volume(s) (PTV) shall include {*x mm margins for internal movements; set-up uncertainties; …*}.
- The {*optical chiasm; spinal cord; lung; kidney; rectum; …*} shall be delineated as Organ(s) at Risk (OAR) based on {*QUANTEC recommendations; anatomical atlas; …*}.
- The Planning Organ-at-Risk Volume(s) (PRV) for the {*optical chiasm; spinal cord; …*} shall be delineated using [*x*] mm margins.
- The volumes shall be delineated with {*grey scale window centre and width*}.
- The smallest volume that is allowed is {*size*}.
- The volumes shall be delineated in {*slices; phases of the breathing cycle; …*}.

Planning aims and dose-volume constraints

- Absorbed dose prescription
  - o The prescribed total absorbed dose is [*D*] Gy, specified as {*median dose to target volume(s); dose to a reference point; dose-volume objectives; …*}.
  - o For treatment planning optimisation, {*physical; biological*} objectives and constraints shall be prioritised according to {*prescription priority list*}.
- Fractionation and treatment time
  - o Radiotherapy is given {*daily; BID; every other weekday; …*} with [*N*] fractions of [*d*] Gy.
  - o The minimum time between daily fractions is [*t*] hours.
  - o Boost is given {*sequential; concomitant; simultaneous*}.
  - o The overall treatment time shall be minimum [N] days and maximum [N] days.

Treatment planning

- The radiation treatment shall be given with {*radiation type; beam quality; dose rate*} and {*3DCRT; IMRT; VMAT; HT; …*} technique.
- Treatment planning technique and machine dependent constraints shall be documented in {*treatment planning manual*}.
- Treatment planning on time-resolved images shall be based on {*largest PTV extent; gating; tracking; …*}.
- The choice of the final treatment plan shall be documented by {*dose-volume summary; fulfilment of objectives and constraints; …*} and reported according to ICRU {*level 2; level 3*}.

Dose computation

- Absorbed dose calculations shall be performed on {*image set*}.
- The calculation grid shall have {*3D size and resolution*}.
- The absorbed dose in the patient geometry shall be calculated by using {*analytical algorithm; MC; …*}, and presented as absorbed dose to {*water; tissue*}.

(Continued)

Table I: Continued.

- Summation of absorbed dose distributions for {*time-resolved images; plan-of-the-day; …*} shall be weighted {*equal; probabilistic; ….*} and mapped using {*rigid registration; deformable registration*}.
- The make and version of the particular treatment planning system and dose calculation algorithm shall be reported. If possible, dose calculation uncertainties shall be reported.

Treatment verification and adaption

- Image-guided treatment delivery
  - o The {*position; shape; size; …*} of the {*patient; target(s); fiducials; OAR(s)*} shall be estimated based on {*EPID; CBCT; MRI; …*}.
  - o The verification shall be performed {*before; during*} the treatment at {*frequency*}, and a statistical analysis shall be performed after {*n; all*} treatments.
  - o Based on the analysis, the treatment delivery shall be adjusted according to {*protocol for corrective action; replanning criteria*}.
  - o The additional absorbed dose contribution due to imaging shall be reported.
- On-line dosimetry
  - o The absorbed dose to the patient shall be estimated based on {*in vivo measurements; in vivo dose reconstruction; …*}.
  - o The verification shall be performed {*during; after completion of*} the treatment at {*frequency*} and a statistical analysis shall be performed after {*n; all*} treatments.
  - o Based on the analysis the treatment delivery shall be adjusted according to {*protocol for corrective action*}.
- Response evaluation
  - o Unintended interruptions shall be compensated within the intended overall treatment time according to {*BED; EQD_x; modified fractionation schedule*}.
  - o Evaluation of {*tumour; normal tissue*} response shall be based on {*CT; PET; MR; CBCT; …*} performed {*timing and frequency*} during the radiotherapy course.
  - o Based on the analysis of the treatment response, the treatment plan shall be adapted by changing {*treatment schedule; modality; …*} in order to {*maximise TCP; minimize NTCP; …*}.

Additional considerations for combined modalities

- Surgery
  - o Radiotherapy is given {*pre-; post-*} operatively.
  - o The intention with the pre-operative treatment is to reduce {*tumour size; risk of loco-regional recurrence; …*}
  - o Radiotherapy shall start [*n*] days/weeks/months {*before; after*} surgery.
  - o Details about the surgical treatment are stated in chapter [*x*] in the treatment protocol.
- Drug therapy
  - o Radiotherapy is given {*pre-; concomitant; post-*} chemotherapy.
  - o Concomitant chemotherapy shall be given [*n*] hours {*before; after*} the radiotherapy fraction.
  - o Details about the chemotherapy are stated in chapter [*x*] in the treatment protocol.

Quality assurance

- Preparatory
  - o Reference dosimetry is carried out according to {*IAEA*, and verified through the {*dosimetry audit programme; …*}.
  - o Dummy run(s) shall be performed before the {*start of study; commissioning of new treatment; …*}, including {*data integrity; dosimetry benchmark; …*}.
- Pre-treatment patient specific QA
  - o Individual case review shall be performed for {*N cases; all cases*}.
  - o The monitor unit calculation for each new patient shall be independently verified with {*independent calculations; measurements*}.
  - o The delivery shall be compared to the plan, and analysed with {*absorbed dose difference; DTA; gamma evaluation; …*} using {*acceptance criteria*}.
  - o In case a plan is not passing the acceptance criteria, the reasons shall be further analysed, and {*replanning; change of technique; ….*} shall be considered.

Finally, we have added one section in this template corresponding to chapter 3 in the EORTC recommendation regarding quality assurance. We encourage the use of the EORTC quality assurance levels, although they are not explicitly specified in the template as some of the levels are primarily designed for EORTC ROG multi-centre trials. This section also includes items regarding independent monitor-unit calculations.

In addition, we have included items regarding in vivo dosimetry, the estimation of dose calculation uncertainties, and suggestions for standardised naming convention of target and organs-at-risk volumes, as recently proposed, e.g. by international radiotherapy societies [9,10].

In conclusion, the present report provides a detailed framework and a recipe-style template, based on an analysis of the contemporary radiotherapy process, including clinical as well as physical aspects. A preliminary version was distributed in 2013 to radiotherapy practitioners in Swedish radiotherapy centres and tested in actual protocol writing situations, and their experience was incorporated in the final version. While the EORTC recommendations are specifically designed for writing EORTC ROG study protocols, we believe that the template presented here should be applicable also for clinical guidelines, care programmes, irrespective of treatment intention and complexity.

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References

[1] Peters LJ, O'Sullivan B, Giralt J, Fitzgerald TJ, Trotti A, Bernier J, et al. Critical impact of radiotherapy protocol compliance and quality in the treatment of advanced head and neck cancer: Results from TROG 02.02. J Clin Oncol 2010;28:2996–3001.

[2] Abrams RA, Winter KA, Regine WF, Safran H, Hoffman JP, Lustig R, et al. Failure to adhere to protocol specified radiation therapy guidelines was associated with decreased survival in RTOG 9704 – a phase III trial of adjuvant chemotherapy and chemoradiotherapy for patients with resected adenocarcinoma of the pancreas. Int J Radiat Oncol Biol Phys 2012;82:809–16.

[3] Fairchild A, Bar-Deroma R, Collette L, Haustermans K, Hurkmans C, Lacombe D, et al. Development of clinical trial protocols involving advanced radiation therapy techniques: The European Organisation for Research and Treatment of Cancer Radiation Oncology Group approach. Eur J Cancer 2012;48:1048–54.

[4] Bolla M, Bartelink H, Garavaglia G, Gonzalez D, Horiot JC, Johansson KA, et al. EORTC guidelines for writing protocols for clinical trials of radiotherapy. Radiother Oncol 1995;36:1–8.

[5] Report from SSM's scientific council on ionizing radiation within oncology, 2011. SSM Report number 2012:20 (ISSN: 2000-0456). Available from: http://www.stralsakerhetsmyndigheten.se/Publikationer/Rapport/Stralskydd/2012/201220/. Cited on 1st September 2014.

[6] Report from SSM's scientific council on ionizing radiation within oncology, 2012. SSM Report number 2014:03 (ISSN: 2000-0456). Available from: http://www.stralsakerhetsmyndigheten.se/Publikationer/Rapport/Stralskydd/2014/201403/. Cited on 1st September 2014.

[7] Petersson K, Gebre-Medhin M, Ceberg C, Nilsson P, Engström P, Knöös T, et al. Haematological toxicity in adult patients receiving craniospinal irradiation – Indication of a dose-bath effect. Radiother Oncol 2014;111:47–51.

[8] Petersson K, Nilsson P, Engström P, Knöös T, Ceberg C. Multi-modality optimisation in radiotherapy treatment planning using composite objective values. Acta Oncol online on September 1, 2014. doi:10.3109/0284186X.2014.953255

[9] Santanam L, Hurkmans C, Mutic S, van Vliet-Vroegindeweij C, Brame S, Straube W, et al. Standardizing naming conventions in radiation oncology. Int J Radiat Oncol Biol Phys 2012;83:1344–9.

[10] En standardiserad svensk nomenklatur för strålbehandling. SSM Report number 2014:25 (ISSN: 2000-0456) (in Swedish). Available from: http://www.stralsakerhetsmyndigheten.se/Publikationer/Rapport/Stralskydd/2014/201425/. Cited on 1st September 2014.

Supplementary material available online

Supplementary Table I to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.981285.