METHODOLOGY: PENTEC ORGAN-SPECIFIC REPORTS

Goal of this document

This document is intended to provide guidance on the proposed steps of the review process and includes examples for several of the steps.

Proposed PENTEC Methodology Summary

See full methodology Sections below for more details

The protocol will describe the following components:

1. Title, authors and roles for each Organ-Specific Report (OSR)

2. Research questions and definitions of clinical outcomes (please refer to section 3.1 and Box 2 in the Methodology Document)

3. Initial inclusion and exclusion criteria (please refer to Appendix IV in the full Methodology Document)
   - Study design
   - Patient groups
   - Radiation assessment definition
   - Outcomes

4. Literature search (please refer to Section 4 in the Methodology Document)
   - Which databases
   - Search terms: In collaboration with the chapter Lead Author (LA), Leontien Kremer and Cecile Ronckers (pentecsearch@gmail.com) will coordinate a draft strategy, including proposed key words and synonyms.

5. Selection process for relevant papers
   - Based on inclusion and exclusion criteria mentioned above
   - Modification based on abstracts/reports obtained (i.e. search modifications may be necessary)

6-8. Data extraction and analysis plan

9. Reporting / manuscript

BOX 1. PENTEC Core Group

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Detailed methodology Document

1. State the PENTEC section title and its authors, including the roles of each member.

2. Develop the research questions and inclusion and exclusion criteria in a brief outline

Each OSR group will prepare a description of their research questions, including identification of the patient group of interest & organ-specific clinical outcomes to be studied in that report, and precise inclusion and exclusion criteria

2.1 Research questions and clinical outcomes

For most reports there will be more than 1 clinically relevant side effect (endpoint). It will be important to make a choice for clinically relevant outcomes with a clear definition.

The International Guidelines Harmonization Group (IGHG-www.ighg.org) has developed proposed clinical outcomes for several organs already, which can serve as starting point for developing PENTEC research questions. The IGHG-versions can be made available to Lead Authors by Leontien, Cecile or Sandy.

BOX 2. Example research question

For example, for the report on male reproductive system, one of the clinically-relevant side effects is related to androgen deficiency and spermatogenesis. The precise research questions of interest can then be defined as:

- "What is the association between radiation dose/volume and the risk of androgen deficiency, defined as low testosterone and/or high FSH, in male childhood cancer survivors treated with radiotherapy involving the testes?
- "What is the association between radiation dose/volume and impaired spermatogenesis, defined as azoospermia and oligospermia, in male childhood cancer survivors treated with radiotherapy involving the testes?

There may be studies that describe the clinical outcome in terms of inhibin B levels; It should be discussed within the author group if these studies should be included. Within the International Guideline Harmonisation Group (IGHG) for surveillance of childhood cancer survivors (www.ighg.org), we decided that these studies will not be included because this measure was shown not to be a suitable surrogate marker of sperm concentration (Green et al, 2013)..These examples are meant to serve as proposals that should be discussed in the organ-specific working groups.

3. Inclusion and exclusion criteria

Please refer to Appendix IV for a proposed list of general inclusion and exclusion criteria. These can be amended on a report-by-report basis, by the respective author

groups, because there will be differences in the amount and type of reports available depending on the organ or clinical outcome of interest.

Brief outline/proposal

Once the research questions, including a description of the patient group of interest & organ-specific clinical outcomes to be studied in that report, and precise in- and exclusion criteria have been prepared, they will be collated into a brief proposal. Since we are striving for some consistency amongst the reports, we are requesting that the lead authors send the proposal along with their list of collaborators to Leontien Kremer and Cecile Ronckers with a copy to Sandy Constine and Lisa Chen (email addresses: see box). After review by selected representatives of the Core Group, for the purposes of offering advice, the OSR reviewers can initiate the next phase: the Search Strategy.

4. Develop a Search Strategy

Goal of the search strategy

To identify as many as possible of the relevant papers in PubMed, we propose to use a well- defined, systematic search strategy. We have developed a general template for a search strategy including 3 basic search terms (Box 3).

BOX 3: Example Pubmed search strategy

Radiotherapy AND Childhood Cancer AND Hearing Loss

Definitions

1. Childhood cancer
(((leukemia OR leukemi* OR leukaemi* OR ALL OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom*) OR (pediatric oncology OR paediatric oncology)) OR (childhood cancer OR childhood tumor OR childhood tumors)) OR (brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm*) OR (leukemia lymphocytic acute) OR (leukemia, lymphocytic, acute[mh])

2. Radiotherapy
radiometry OR radiation dosage OR radiation dose OR radiation doses OR radiation dosis OR radiation dosage* OR radiation dosimetry OR radiation dosimetr* OR dose-response relationship, radiation OR radiometr* OR radiotherapy dosage OR radiotherapy[sh] OR radiotherapy/adverse effects OR irradiation dose OR radiotherapy dose OR dose calculation OR near beam dose OR in beam dose OR outside beam dose OR out of beam dose OR radiation/epidemiology OR Radiation monitoring OR Organs at risk OR radiation effects[sh] OR radiation injury OR radiation injuries OR radiation OR Radiotherapy/complications[Mesh] OR NCTP OR normal tissue complication probability OR DVH OR Dose Volume Histogram OR Radiotherapy Planning OR Conformal/adverse effects OR Dose Response Relationship, radiation OR Organs at Risk/Radiation Effects OR Radiation Injuries/Prevention and Control OR Chemoradiotherapy/Adverse Effects

Example outcome:

3. Hearing Loss

Deafness OR hearing loss OR Loss, Hearing OR hearing disorder OR hearing disorders OR auditory OR hearing impairment OR hearing impairments OR hearing impairment* OR heari* OR audiology OR audiologic OR audiometry OR audiometr* OR audiogram OR audiography OR ototoxicology OR ototoxic* OR hypoacusis OR hypoacuses OR hypoacus* OR ototoxicity OR deaf* OR cochleotoxicity

Result in Pubmed (Sept 23,2013): n=544 reports fulfill these criteria, and are therefore eligible for title/abstract screening

STEPS to develop a search strategy

a) The chapter Lead Author (LA) will send the approved outcomes list to **Leontien Kremer (Chair Cochrane CCG)** and **Cecile Ronckers (Epi Core Chair)** at **pentecsearch@gmail.com**. They will coordinate correspondence and work flow with the experienced Cochrane Childhood Cancer Group (Cochrane CCG) trial search coordinator, Ms. **Edith Leclercq**
b) In collaboration with the chapter LA, Leontien, Cecile and Edith Leclercq will propose a draft strategy (see ref 1,2 for examples and methodology), including proposed key words. The template will then be modified in close collaboration with the OSR authors (represented by the LA) for each individual group/report
c) Final searches using the key words finalized in step b) will then be run in PubMed either by Edith Leclercq of the Cochrane group or by the group LA's themselves, according to their preference. This action will then generate a list of abstracts. If the search is run by Edith from the Cochrane Childhood Cancer Group, the abstracts can be delivered to the organ group LA as a word file, an endnote file, or as Reference manager library, according to LA's preferences.

NOTE
For each OSR, the final search strategy will be published/shown separately (as an appendix and/or online supplement) so the process is transparent.

5. Select eligible papers/studies

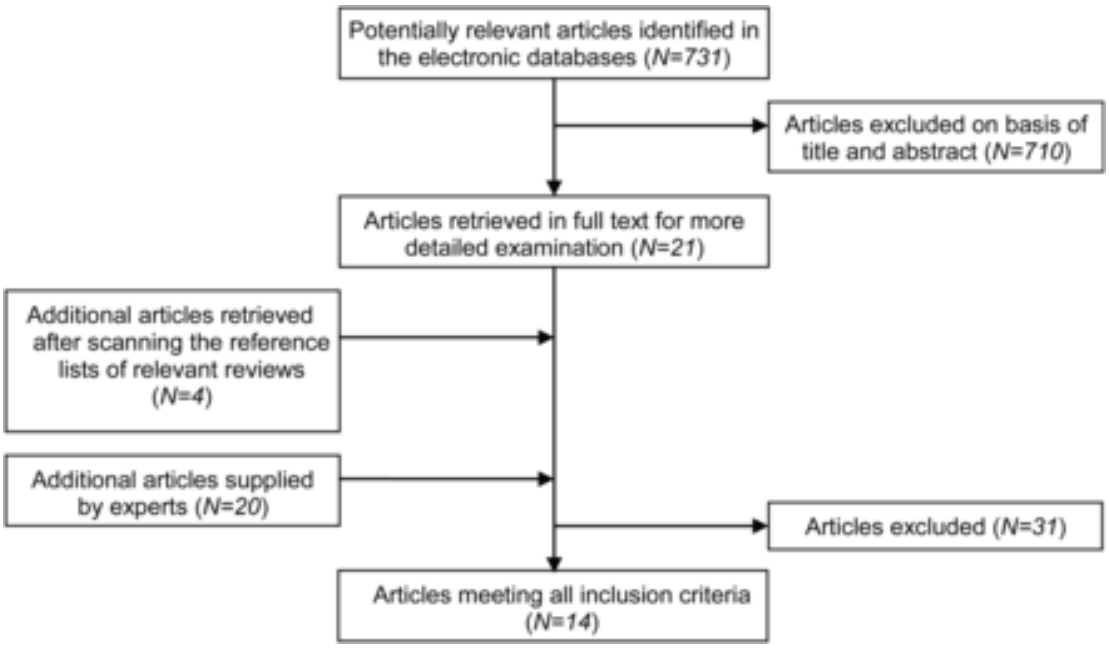
The reviewers will select papers from the generated list of abstracts based on in- & exclusion criteria. In this process, it is important to be initially inclusive of reports that may not have dose/volume data in the most ideal format; if many papers with NTCP-type data are available, the authors may choose to exclude papers with less detailed information. This should be specified in the inclusion criteria and is up to the discretion of the respective report authors. In general the PENTEC effort is intended to summarize the available evidence on radiation treatment and organ-specific outcomes; if it is not possible to build a complete pooled NTCP model, it is still very valuable to summarize other type of dose/volume data or report actuarial incidence of complications.

STEPS to select eligible papers

a) Reviewers select potentially eligible papers based on title and abstract review. All abstracts are then classified as follows: preliminary inclusion, or exclusion, or unclear; *It is important that the 2 reviewers do this independently*.
b) Compare the results and discuss discordances between the 2 reviewers.
c) For all *preliminary inclusions* and *unclear abstracts* the full-text papers (pdf's). are then retrieved and the finally included papers are selected by full text review, again by 2 reviewers.

d) Compare the results and discuss discordances between the 2 reviewers; in case a consensus cannot be reached, involve an arbiter (third reviewer from same OSR).
e) Select references from excellent reviews.
f) Select additional papers from experts in the field known to the reviewers that did not appear in the Pubmed search. If these papers fulfill all inclusion criteria, they will be considered as full papers for the OSR and possible pooled analyses, similar to the other selected papers/studies.
g) Consider selecting references from the "assigned citation index" in Pubmed
h) It is recommended to summarize the in- & exclusion of papers in a flow diagram; (Box 4)

BOX 4: Example flow diagram to show included and excluded studies



6. Data extraction and quality assessment

Steps to extract data from original papers

a) The reviewers who are responsible for the selection process will complete the PENTEC data extraction form (see below) for all finally included papers/studies; The PENTEC data extraction form is shown in Appendix II (p 11-12). The detailed PENTEC instruction / FAQ document is added as Appendix III (pages 17-22)
NOTE: It is not necessary that the same 2 individuals cover all papers/studies; that is, the task can be divided between several members of a organ-report group.

b) The reviewers will summarize the evidence from included studies in a brief summary table (equivalent to Table 1 in the QUANTEC series—see appendix V but with an additional column that denotes "Age Dependency") and will comment on general aspects of quality of the study such as selection bias or follow-up bias; advice can be obtained from the epidemiologists and other methodologists in the Core Group. An example of the summary table that will be created for each OSR is shown in Box 5. Such a table will provide another level of consistency amongst the 18 OSR's and be a unique resource for readers. In addition to preparing such a table, we will request the lead authors to summarize their OSR data into a few lines similar to those in appendix V, but with the addition of an "age dependency" column.

BOX 5: Variables to be included in a Summary Table within each OSR

- First author, year of pub (ref nr)
- Study Design
- Childhood cancer diagnosis group
- Calendar year of diagnosis
- Age at treatment of childhood cancer
- Follow-up duration
- Radiotherapy technique
- Radiotherapy fields
- Cumulative physical dose (mean/median, min-max)
- Chemotherapy regimens
- Outcome assessment methods
- Outcome incidence
- Primary toxicity predictor
- Other risk factors

Optional

- Completeness of follow-up (%)
- Multivariable analyses y/n

It is acknowledged that some parameters may not be possible to extract for all OSR's, but the groups should strive to complete this table to the degree possible.

In addition, the conclusions of evidence should be qualified according to pre-specified criteria for levels of evidence" based on the International Harmonization Group (www.ighg.org).see ref 4. , as shown below:

BOX 6: Level of Evidence Scoring

Conclusions of evidence	Study quality	Wording in conclusions
A High level of evidence	Evidence from well performed and high quality studies or systematic reviews (low risk of bias, direct,* consistent, precise)	'There is evidence that…'
B Moderate/ Low level of evidence	Evidence from studies or systematic reviews with few important limitations	'Evidence suggests that…'
C Very low level of evidence	Evidence from studies with serious flaws (high risk of bias, indirect, inconsistent, imprecise)	'Some evidence suggests that…'
Conflicting evidence	N/A	'There is conflicting evidence…'
No evidence	N/A	'No studies reported on…'

Direct evidence comes from research that directly compares the interventions in which we are interested and measures outcomes important to patients. Studies are indirect if there are differences in study population (our population of interest is childhood cancer survivors), interventions, or outcome measures

7. Review of selection of papers and extraction tables

We request that the organ-report reviewers send the results of the selection of papers, i.e., the flow chart, and all completed extraction tables, to the member of the central review group (a subcommittee of the PENTEC Core Group) assigned to that respective organ-report, for a brief review. The main purpose of this step is to provide additional expertise in judging the potential biases in the study report, which will aid the selection of eligible studies, and the assignment of levels of evidence for study reports and final conclusions; this is not meant to check any single number in the extraction tables.

8. Data analysis phase

Once the study selection and data extraction have been completed and briefly reviewed, we propose the following steps for the data analysis phase:

a) The modeling physicist runs preliminary data checks and analyses, to evaluate the completeness of the data as well as possible heterogeneity, and to test various possibilities to model or otherwise summarize the available dose-response information. If the available data are not sufficiently detailed to build full pooled NTCP models, the group can choose the most appropriate way to

summarize and graphically depict the available information as they see fit. NCTP models are the ideal goal; however, absence of an NCTP model does not mean failure of the report. The aim of our effort is to collate all available information to help clinicians make informed, evidence based choices when planning a radiotherapy treatment. It is worth noting that any models for which parameters are estimated and presented should also be validated through the appropriate goodness-of-fit analysis or regression diagnostics.

b) In collaboration with the OSR LA and (if available) the OSR epidemiologist, the modeling physicist prepares a brief Analysis Proposal. This brief document is intended to summarize what data are potentially available for analysis, what the issues are, what type of quantitative summary is expected to be most appropriate (given the available data), and what can eventually be said about the organ side effect of interest. The Analysis Proposal is then submitted to the following representatives of the Core Group for review: Andy Jackson, Søren Bentzen, Leontien Kremer and Cécile Ronckers, with copy to Sandy Constine (email addresses see above). This process is meant to support the author groups, and to share experiences across the PENTEC organ specific groups.
c) After review and, if necessary, a phone conference, the modeling physicist can run the full analyses
d) For a number of chapters it is anticipated that little detailed data on dose/volume relationships are available in the published literature to date. This is recognized by the Core Group and should not hamper LA 's from developing a proposal to summarize / synthesize the available data in a meaningful way. The goal of the organ-specific report is to provide a comprehensive summary of the current state of evidence regarding that organ, to provide guidance to clinicians who treat childhood cancer patients. Please also refer to Appendix I, the outline of sections for each report, in particular section #6.

The analysis of mixed data from dose-volume-based studies and epidemiologic late effects studies, typically concerning prescribed dose or average absorbed dose for normal tissues) can pose certain challenges. This issue and other pitfalls have been documented below, including potential solutions.

9. Reporting / manuscript

The OSR LA will prepare a manuscript in collaboration with all group authors. The required sections and elements of the manuscript are described in Appendix I. The draft manuscript will be submitted for review to the Core Group prior to journal submission.

10. Proposed Timeline

Data Extraction: 6 months
First Draft submitted to steering committee: 12 months
Final draft reviewed by the steering committee: 18 months

References

1. Lundh A, Kremer LCM, Leclercq E. Tips and tricks for understanding and using SR results. No. 6: development of a search strategy. Evid.-Based Child Health 2007;2: 937–939.
2. Leclercq E, Leefland MMG, van Dalen EC, Kremer LCM. Validation of Search Filters for Identifying Pediatric Studies in PubMed. J Pediatr 2013: 162:629-34.
3. Green DM, Zhu L, Zhang N, Sklar CA, Ke RW, Kutteh WH, Klosky JL, Spunt SL, Metzger ML, Navid F, Srivastava D, Robison LL, Hudson MM. Lack of specificity of plasma concentrations of inhibin B and follicle-stimulating hormone for identification of azoospermic survivors of childhood cancer: a report from the St Jude lifetime cohort study. J Clin Oncol. 2013 Apr 1;31(10):1324-8.
4. Kremer LC, Mulder RL, Oeffinger KC, Bhatia S, Landier W, Levitt G, Constine LS, Wallace WH, Caron HN, Armenian SH, Skinner R, Hudson MM; International Late Effects of Childhood Cancer Guideline Harmonization Group. A worldwide collaboration to harmonize guidelines for the long-term follow-up of childhood and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Pediatr Blood Cancer. 2013 Apr;60(4):543-9.

Appendix I

Sections within each organ-specific report (OSR):

1. Anatomy and developmental dynamics

- Define anatomy as it impacts normal tissue damage
- Describe anatomic and physiologic development according to age as it impacts organ sensitivity to damage and repair

2. Clinical significance

- Describe the clinical situations where the organ is irradiated
- Briefly describe the frequency, characteristics, significance of injury.

3. Endpoints and Toxicity Scoring

- Address strengths and limitations of existing systems
- Recommend how to score organ injury
- Describe the different endpoints often considered when assessing injury, the impact of endpoint-selection on the reported injury rates, the challenges/utilities of different endpoints, and the time course of organ injury.

4. Challenges defining volumes: pediatric imaging issues

- Describe recommended imaging modality and acquisition methods (e.g. contrast enhanced, slice thickness/spacing, slice orientation, pulse sequence).
- Discuss the impact of intra-/inter-fractional organ movement or volume change during the course of treatment.
- Discuss the need for contouring planning organ-at risk volumes (PRV).
- Note normal organ contouring atlases or reference existing publically available atlases. Give specific guidance on difficult organs to contour, like the hippocampus.

5. Review of Dose Volume response data and risk factors

- **Review of dose-volume data –** For each organ (tissue), published data on toxicity risks, as correlated with dosimetric parameters and other relevant variables (i.e. age, developmental status), are reviewed. From the available data, meaningful dose/volume limits with associated risk rates are presented. Include data on various dose fractionations, adequacy, quality, and bias.
- **Dose Volume Endpoints:**
    - **Organ Function:** Lab/subclinical endpoints, imaging endpoints, physiologic/functional issues
    - **Organ Development:** Impact of age
    - **Second malignant neoplasms: dose response data looks different in each organ section).**
- **Risk Factors:** genetic predispositions, gender, race, age, co-medical conditions
- **Chemotherapy/Combined modality:** Relevant chemo data impacting

radiation sensitivity

- **Mathematical/Biologic models + Epidemiologic issues**: For each organ, models that have been used to relate dose/volume data to normal tissue complications and second malignancies in the organ are summarized, along with associated model parameters, limitations and uncertainties. Note: If the available data are not sufficiently detailed to build NTCP models, the credible data should still be summarized (e.g. actuarial incidence of complications)

6. **Recommended dose volume** (Dose per fraction)
    - **Recommended Dose/Volume Limits**- The available information is condensed into meaningful dose/volume limits, with associated risk rates, for clinical application. Limits are according to endpoints and age. It is recognized by the Core Group that detailed dose/volume data may not be available for all organs of interest. The reports are intended to provide a comprehensive overview of relevant data and can include statements about the perceived tolerance doses/volumes/fractions based on the literature and clinical experience
    - **Specify the level of evidence for each report (see Box 6 in "Methodology")**
    - **Special situations**: most of the data discussed relates to conventional fractionation. This section describes situations where the presented data/models may not apply (e.g. hypofractionation)
7. **Toxicity scoring recommendations**
    - Recommendations on how to score organ injury and toxicities.

8. **Interventions and Management**

9. **Contrast Pediatric and Adult NTCP data**

10. **Future investigations**
    - Describes areas in need of future study

Appendix II
PENTEC Data Abstraction/Collection Form

1	Reviewer Name:				
2	Reference (Author, Title):				
2.1	PubMed ID/Link				
3	Endpoint:	# of Endpoints:			
4	Study classification:	Click for menu			
5	Organ/anatomical region:	Click for menu	Click for menu		
6	Is radiation dose response analyzed according to developmental status? Comments:	Yes☐	No☐		
7	Delineation of OAR described in paper: Comment:	Yes☐	No☐		
8	Primary Cancer	Specify:			
9	**Eligibility/Exclusion Criteria**				
9.1	Length of Follow up:	Yes☐	No☐	NR☐	Specify:
9.2	Age at time of childhood cancer diagnosis:	Yes☐	No☐	NR☐	Specify:
9.3	Age at time of evaluation/follow-up:	Yes☐	No☐	NR☐	Specify:
9.4	Calendar period of childhood cancer treatment:	Yes☐	No☐	NR☐	Specify:
9.5	Other:	Yes☐	No☐	NR☐	Specify:
9.6	Comments for items #1-#9:				
10	**Patient Numbers**				
10.1	Total number of eligible patients:				
10.2	Number of patients analyzed in study:				
10.3	Number of events for the relevant endpoint:				
11	**Scoring of Side-effects**				
11.1	Grading system:	Click for menu NR☐			
11.2	Type of endpoint analyzed:	Click for menu NR☐			
11.3	If ordinal endpoint is dichotomized, threshold grade for calling an event:	Click for menu NR☐			
11.4	Method of outcome evaluation				
11.4.1	Clinical Assessment				
11.4.1a	Physical examination	Yes☐	No☐	NR☐	
11.4.1b	Imaging	Yes☐	No☐	NR☐	
11.4.1c	Functional Imaging	Yes☐	No☐	NR☐	
11.4.1d	Laboratory test	Yes☐	No☐	NR☐	
11.4.1e	Other Analytic test	Yes☐	No☐	NR☐	

11.4.2	If 11.4.1. = yes: Corrected for baseline value?	Yes☐ No☐ NR☐	
11.4.3	Self-report only	Yes☐ No☐ NR☐	
11.4.4	Self-report with medical validation	Yes☐ No☐ NR☐	
11.4.5	Registry-linkage based	Yes☐ No☐ NR☐	
11.5	Endpoint classification (check all that apply)		
	☐ Incidence ☐ Prevalence ☐ Mortality ☐ Other -Please specify:		
11.6	Method used to adjust for latency:	Click for menu	
11.7	Comments for section #11:		
12	**Radiation Therapy: Prescribed dose fractionation**		
12.1	Total Prescribed Dose (Gy):		
12.1.1	Dose per fraction (Gy)	Min: Max:	
12.1.2	Planned overall time (days)	Min: Max:	
12.2	Dose Prescribed to:	Click for menu	
12.3	Dose distribution derived from:	Click for menu	
13	**Radiation therapy: Technical aspects**		
13.1	Radiation technique: (check all that apply)		
	☐ NR ☐ Parallel opposing photon fields or similar simple arrangements Energy: ☐ KV ☐ MV ☐ Brachytherapy ☐ Particle Therapy Comment:	☐ Various ☐ 3D-CRT ☐ IMRT ☐ Stereotactic or SBRT ☐ Electrons	
13.2	Heterogeneity correction in dose calc:	Click for menu ☐	NR
13.3	Comments for sections #12 and #13		
14	**Chemotherapy (check all that apply):**		
	☐ Not used ☐ Alkylating agents ☐ Anthracyclines ☐ Bleomycin ☐ Corticosteroids	☐ Unknown ☐ Vinca Alkoids ☐ Epipodophyllotoxins ☐ Other	
14.1	Bone Marrow Transplant If Yes, conditioning with TBI	Yes☐ No☐ NR☐ Yes☐ No☐ NR☐	
14.2	Drug and/or BMT effect analyzed in paper	Yes☐ No☐ NR☐	

15	**Data analytic approach (up to 3):**		
	☐ Comparison of outcome in two or more groups		
	☐ Use of previously published model/parameters		
	☐ "Statistical modeling" (Cox, Logistic regression, cumulative incidence)		
	☐ Other method ☐ NR		
	Specify:		
15.1	Were dose Volume descriptors analyzed?	Yes☐ No☐ NR☐ Specify:	
15.2	Dose-volume descriptors found to be significant?	Yes☐ No☐ NA☐	
15.3	Parametric dose-volume modeling?	Yes☐ No☐ NR☐	
15.3.1	Specify Model:	Yes☐ No☐ Comment:	
15.3.2	Specify Model validation:	Yes☐ No☐	
15.4	Comments:		
16	**Patient Age and Follow-up**		
16.1	Length of Follow-up (mean, median, and range):		
16.2	Age at diagnosis (mean, median and range):		
16.3	Age attained at end of follow-up (mean, median, and range):		
16.4	Comment:		
17	**Variables considered in analysis**		Significance:
17.1	Age at Diagnosis	Yes☐ No☐	Yes☐ No☐
17.2	Attained Age	Yes☐ No☐	Yes☐ No☐
17.3	Gender	Yes☐ No☐	Yes☐ No☐
17.4	Race	Yes☐ No☐	Yes☐ No☐
17.5	Genetic Abnormality	Yes☐ No☐	Yes☐ No☐
17.6	Other	Yes☐ No☐	Yes☐ No☐
	Specify:		
17.7	Co-morbidity	Yes☐ No☐	Specify:
17.8	Lab tests	Yes☐ No☐	Specify:
17.9	Other patient related factors considered in the analysis:		
17.10	Calendar years of childhood cancer treatment:		
18	Bio-banking or biomarkers assessed:	Yes☐ No☐	
19	**Major source of variation in dose-volume histogram:**		
	☐ Not clear from paper		
	☐ Inter-individual variation in anatomy and target definition		
	☐ Change in treatment policy over time		
	☐ Varied prescription according to patient/disease factors		
	☐ Randomized allocation to different treatments		
	☐ Minimal variation of dose-volume parameters		
20	Author's conclusion:		
20.1	Significant volume effect	Yes☐ No☐	
20.2	Significant dose response	Yes☐ No☐	
20.3	Recommended dose-volume constraint:		

Appendix III
Instructions and FAQ for chapter authors on PENTEC Data Abstraction Form

PENTEC Review Form Instructions:

The following Instructions sheet accompanies the data (report) review form that should be completed for each report that is analyzed. These forms will have multiple purposes:

1. To aid you in determining which reports are valuable, and their strengths and weaknesses that impact on their value.
2. To assist in summarizing the important data, and the limitations of that data, as you proceed with analysis of your organ.
3. To serve as a piece of data that will be used by members of the core committee to evaluate the data collection process used in this PENTEC effort.

You will notice that comprehensive completion of this form will require the expertise of the various members of your group (radiation oncology, subspecialists, epidemiologists, physicists including normal tissue modelers). You may chose to distribute the data review form to all members with specific assignments for each, to request that all members fill out the form to the best of their ability, or have conference calls (or similar methods of communication) to review the form together.

If you find that some component of the form is too difficult to complete, or not applicable, we propose to discuss the problem with your chapter epidemiologist or contact a member of the Epidemiology Core via c.m.ronckers@amc.nl. For unresolved issues, please proceed with the other elements and skip the item in question.

1. Reviewer:
(Name(s): Last, First)

2.Reference:
(1st Author; Journal; Vol: Start page; Year)

2.1 PubMed ID/Link:

Example: PMID 8416438

Or http://www.ncbi.nlm.nih.gov/pubmed/8416438

3. Endpoint: # of endpoints:

List endpoint or endpoints for which form is being filled out. A paper may have multiple endpoints, in which case (1) separate forms can be filled out for each endpoint or (2) similar endpoints can be reviewed in one form.

4. Study Classification:

M: Meta Analysis

RCT-P: RCT with prospective follow-up for adverse events

OPP: Observational study based on a cohort with real-time accrual and prospective follow-up for adverse events;

RCT-R: RCT done in the past with one-time retrospective assessment of adverse events.

ORP: Observational study based in a cohort or patient series treated in the past (retrospective) with prospective

follow-up for adverse events.

ORR: Observational study based on a cohort or patient series treated in the past with retrospective follow-up for

adverse events (medical chart based or questionnaire based or record linkage based)

Other

5. Organ/anatomical region:
(Organ from list)

Choose organ from list. This reflects the relevant PENTEC review which this endpoint falls under. An example: neurocognitive outcomes would fall under "Brain"

6. Is Radiation dose response analyzed according to developmental status?:
(Yes/No)

The anticipated late toxicity of cancer therapy is related to the patient's developmental status (i.e. age). The affect of age may vary (both in extent of the effect, and age range for which effect is most important) between different organs. This question is simply asking if the paper addressed developmental status in their analyses of late toxicity.

7. Delineation of OAR in paper: (Y/N)
Comment: If organ at risk (OAR) was partitioned into sub volumes, (i.e. renal pelvic versus renal cortex; whole heart versus left ventricle please note this in comments) (See section 15.1 and 15.4)

The manner in which an organ is delineated may be different between different studies. Example would be definition of the cord as the thecal sac, or true cord (as defined in MRI); definition of the heart as all soft tissue within the pericardium or just the left ventricle. This question asks if the manner in which the organ was delineated is explained, and has an option for a description of this in the comments section.

8. Primary Cancer:
Specify:

List the primary cancer(s) included in this study

9 Eligibility/Exclusion Criteria:

This section describes criteria used for determining if a patient was included in the study.

9.1 Length of Follow-up:

Yes/No/NR (not reported):

Specify:

This queries whether length of follow-up was used as criteria for inclusion (NOT whether follow-up was reported)

9.2 Age at time of childhood cancer diagnosis:

Yes/No/NR (not reported):

Specify:

This queries whether age at time of cancer diagnosis was used as criteria for inclusion (NOT whether age was reported)

9.3 Age at time of evaluation/follow-up:

Yes/No/NR (not reported):

Specify:

This queries whether attained age at time of evaluation of toxicity was used as criteria for inclusion (NOT whether this age was reported)

9.4 Calendar period of childhood cancer treatment:

Yes/No/NR (not reported):

Specify:

This queries whether attained years/decades/eras at time of cancer diagnosis was used as a criteria for inclusion (i.e. patients treated from 1980-1990)

9.5 Other:

This queries whether any other variables were used as a criteria for inclusion (i.e. geographical region, gender, only those treated with radiation alone …)

10. Patient Numbers:

10.1 Total number of eligible patients: (number)

This may include patients who were not analyzed, but from which study cohort was derived.

10.2 Number of patients analyzed in study:

(Number)

If not all patients were analyzed, this allows recording how many were.

This refers to the number of patients whose data were actually included in the stats analysis.

10.3 Number of events for the relevant endpoint:

(Number):

11. Scoring of Side Effects:

11.1 Grading System:
(Menu) or NR

If a grading system was used to score toxicity, please choose the appropriate one here, or if not reported/not relevant check the NR box.

11.2 Type of Endpoint analyzed:
(Menu) or NR

Dichotomous- i.e. binary: yes/no, 1/0 etc.
Ordinal- i.e. grouped into whole numbers: any of the grading systems
Continuous- i.e. endpoint in quantified as a number along a continuum (i.e. quantifiable blood test or analytic functional assessment).

If no clinical endpoint considered, go to 11.4

11.3 If ordinal endpoint is dichotomized, threshold grade for calling an event:
(Menu) or NR

Example: event is considered grade 4-5 toxic event. This represents an ordinal endpoint (5 point scale for toxicity grade) split into a binary endpoint: grade 1-3 versus grade 4-5.

11.4 Method of outcome evaluation:
If Yes, endpoint corrected for baseline value

Click all that apply to the endpoint.
Self-report indicates whether questionnaire based information was collected from children, parents, guardians, or from survivors that are adults at the time of assessment.

11.5) Endpoint classification (check all that apply)
11.6) Method used to adjust for latency:
(Menu) or NR

This describes the manner in which actuarial analyses or other means were used to account for the duration of time between diagnosis or end of treatment) until event or time of analysis for event

11.7 Comments for Section 11:

12. Radiation Therapy Prescribed Dose Fractionation:
12.1 Total dose (Gy):
12.1.1 Dose per fraction (Gy): (Min: Max:)
12.1.2 Planned overall time (days): (Min: Max:)
12.2 Dose prescribed to: (menu) or NR
12.4 Dose distribution derived from: (menu) or NR

In some reports, 3D dose-volume data is not available (options 1-3). If the radiation fields, and patient CT are available to reconstruct the plan, option 1 would apply. If the radiation fields were available, and were planned on phantoms mimicking the patient, then option 2 would apply. If the volume of

organ receiving dose is based solely on 2D data (i.e. percent of kidney in the field), then option 3 would apply.

13. Radiation therapy: technical aspects
13.1 Radiation technique: (check all that apply)
13.2 Heterogeneity correction in dose calc: (menu)
13.3 Comments for section 12 and 13:

In the comments section, please feel free to add any relevant details, e.g. cobalt/orthovoltage/LINAC for external beam radiation, radioactive source for brachytherapy, HDR or LDR for brachytherapy, type of IMRT (i.e. VMAT, fixed beam, MLC-based, etc.)

14. Chemotherapy (check all that apply):
14.1 Bone Marrow Transplant (Yes/No/NR)

If Yes, indicate conditioning with TBI: (Yes/No/NR)

14.2 Drug and/or BMT effect analyzed in paper: (Yes/No/NR)

15. Data analytic approach: (check up to 3)
15.1 Were dose volume descriptors analyzed?: (Y/N/NR) (If DVH parameters of organ sub volumes (section 7) were considered for toxicity risks, please note this. For example: Were dose volume descriptors correlated with outcome?)
15.2 Dose-volume descriptors found to be significant?: (Y/N/NA)
15.3 Parametric dose-volume modeling?: (Y/N/NR)
15.3.1 Specify Model (name the model): (Y/N/Comment)
15.3.2 Specify Model validation: (Y/N)
If organ sub volumes (see notes on section 7) or dose distribution geometry within an organ was considered for the analyzed endpoint, please note this in the comments.
15.4 Comments:

16. Patient Age and Follow-up:

Unlike section 9 which describes variable used for inclusion in the study, this section is used to characterize the reported age and follow-up of the study cohort.

16.1 Length of Follow-up: (mean, median, range)
16.2 Age at diagnosis: (mean, median, range)
16.3 Age attained at end of follow-up: (mean, median, range)
16.4 Comment:

17. Variables considered in analysis:
17.1 Age at Diagnosis: (Y/N) and Significance (Y/N) *for all in this section
17.2 Attained Age:
17.3 Gender:
17.4 Race:
17.5 Genetic Abnormality:
17.6 Other/Specify: (Connective tissue disease (RA etc), Hypertension, diabetes, Endocrine dysfunction)

17.7 Co-morbidity: (Y/N) Specify
17.8 Lab tests: (Y/N) Specify
17.9 Other patient related factors considered in the analysis:
17.10 Calendar years of childhood cancer treatment:

18. Bio-banking, bio-markers assessed: (Y/N)

19. Major source of variation of dose-volume histograms: (Check all that apply)
This section describes why there would be variability in the dose-volume parameters for the organ at risk to account for differences in toxicity outcomes.

20. Authors Conclusion:
20.1 Significant volume effect?: (Y/N)
20.2 Significant dose response?: (Y/N)
20.3 recommended dose-volume constraint:

Appendix IV

Proposed general in- and exclusion criteria

These criteria are intended to serve as a general template that can be amended for the specific organ reports as deemed appropriate by the respective group authors:

1. Publication status of reviewed papers: We will include published or In Press papers only
2. Type of study: Human studies only;
3. Type of study: All study designs (no limitation on study design)
4. Study population: no limitation. If for some organ reports the number of included papers is very large, it is up to the discretion of the chapter authors to tighten this inclusion criterion, for example, to exclude case reports, or to exclude studies concerning less than 5, less than 10, or less than 20 patients. The goal of such an additional inclusion criterion is to limit the number of papers for which an extraction form needs to be completed without excluding relevant evidence;
5. Study population: if a study includes mixed-age survivors (i.e., children and adults at time of first cancer treatment) the study report will only be *included* if:
    - The results are reported separately for children and adults, or
    - The stratified results can be provided by the study authors, or
    - The data cannot be split for adults and children*, and* the study included more than 50% children (age <21). These studies on mixed-age survivor populations primarily concern cancers that occur frequently in adolescence and in adulthood, most prominently lymphoma, but also testicular cancer, sarcoma, brain tumors, melanoma and thyroid cancer;
6. Exposure definitions and analyses: Radiotherapy analyses reported in the paper should include irradiated volume, or a dose metric, or both;
7. Analysis: Whenever possible, the radiation dose/volume analysis should be corrected for important confounders as determined by the reviewer group, by multivariable analyses or stratified/subgroup analyses. This criterion may not hold for all organ reports; if the literature is really limited, it may be important to also include studies reporting univariate results only, but then the organ-report text should clearly identify the disadvantages of this method, the likely impact on the interpretation, and the limitations when extrapolating to other patient populations/situations.

Appendix V
NTCP Table 1

Table 1. QUANTEC Summary: Approximate Dose/Volume/Outcome Data for Several Organs Following Conventional Fractionation (Unless Otherwise Noted)*

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Brain	Whole organ	3D-CRT	Symptomatic necrosis	Dmax <60	<3	Data at 72 and 90 Gy, extrapolated from BED models
	Whole organ	3D-CRT	Symptomatic necrosis	Dmax = 72	5	
	Whole organ	3D-CRT	Symptomatic necrosis	Dmax = 90	10	
	Whole organ	SRS (single fraction)	Symptomatic necrosis	V12 <5–10 cc	<20	Rapid rise when V12 > 5–10 cc
Brain stem	Whole organ	Whole organ	Permanent cranial neuropathy or necrosis	Dmax <54	<5	
	Whole organ	3D-CRT	Permanent cranial neuropathy or necrosis	D1–10 cc‖ ≤59	<5	
	Whole organ	3D-CRT	Permanent cranial neuropathy or necrosis	Dmax <64	<5	Point dose <<1 cc
	Whole organ	SRS (single fraction)	Permanent cranial neuropathy or necrosis	Dmax <12.5	<5	For patients with acoustic tumors
Optic nerve / chiasm	Whole organ	3D-CRT	Optic neuropathy	Dmax <55	<3	Given the small size, 3DCRT is often whole organ‡‡
	Whole organ	3D-CRT	Optic neuropathy	Dmax 55–60	3–7	
	Whole organ	3D-CRT	Optic neuropathy	Dmax >60	>7-20	
	Whole organ	SRS (single fraction)	Optic neuropathy	Dmax <12	<10	
Spinal cord	Partial organ	3D-CRT	Myelopathy	Dmax = 50	0.2	Including full cord cross-section
	Partial organ	3D-CRT	Myelopathy	Dmax = 60	6	
	Partial organ	3D-CRT	Myelopathy	Dmax = 69	50	
	Partial organ	SRS (single fraction)	Myelopathy	Dmax = 13	1	Partial cord cross-section irradiated
	Partial organ	SRS (hypofraction)	Myelopathy	Dmax = 20	1	3 fractions, partial cord cross-section irradiated
Cochlea	Whole organ	3D-CRT	Sensory neural hearing loss	Mean dose ≤45	<30	Mean dose to cochlear, hearing at 4 kHz
	Whole organ	SRS (single fraction)	Sensory neural hearing loss	Prescription dose ≤14	<25	Serviceable hearing
Parotid	Bilateral whole parotid glands	3D-CRT	Long term parotid salivary function reduced to <25% of pre-RT level	Mean dose <25	<20	For combined parotid glands¶
	Unilateral whole parotid gland	3D-CRT	Long term parotid salivary function reduced to <25% of pre-RT level	Mean dose <20	<20	For single parotid gland. At least one parotid gland spared to <20 Gy¶

Table 1. QUANTEC Summary: Approximate Dose/Volume/Outcome Data for Several Organs Following Conventional Fractionation (Unless Otherwise Noted)* (*Continued*)

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
	Bilateral whole parotid glands	3D-CRT	Long term parotid salivary function reduced to <25% of pre-RT level	Mean dose <39	<50	For combined parotid glands (per Fig. 3 in paper) ¶
Pharynx	Pharyngeal constrictors	Whole organ	Symptomatic dysphagia and aspiration	Mean dose <50	<20	Based on Section B4 in paper
Larynx	Whole organ	3D-CRT	Vocal dysfunction	Dmax <66	<20	With chemotherapy, based on single study (see Section A4.2 in paper)
	Whole organ	3D-CRT	Aspiration	Mean dose <50	<30	With chemotherapy, based on single study (see Fig. 1 in paper)
	Whole organ	3D-CRT	Edema	Mean dose <44	<20	Without chemotherapy, based on single study in patients without larynx cancer**
	Whole organ	3D-CRT	Edema	V50 <27%	<20	
Lung	Whole organ	3D-CRT	Symptomatic pneumonitis	V20 ≤ 30%	<20	For combined lung. Gradual dose response
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 7	5	Excludes purposeful whole lung irradiation
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 13	10	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 20	20	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 24	30	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 27	40	
Esophagus	Whole organ	3D-CRT	Grade ≥3 acute esophagitis	Mean dose <34	5–20	Based on RTOG and several studies
	Whole organ	3D-CRT	Grade ≥2 acute esophagitis	V35 <50%	<30	A variety of alternate threshold doses have been implicated. Appears to be a dose/volume response
	Whole organ	3D-CRT	Grade ≥2 acute esophagitis	V50 <40%	<30	
	Whole organ	3D-CRT	Grade ≥2 acute esophagitis	V70 <20%	<30	
Heart	Pericardium	3D-CRT	Pericarditis	Mean dose <26	<15	Based on single study
	Pericardium	3D-CRT	Pericarditis	V30 <46%	<15	
	Whole organ	3D-CRT	Long-term cardiac mortality	V25 <10%	<1	Overly safe risk estimate based on model predictions

(*Continued*)

Table 1. QUANTEC Summary: Approximate Dose/Volume/Outcome Data for Several Organs Following Conventional Fractionation (Unless Otherwise Noted)* (*Continued*)

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Liver	Whole liver – GTV	3D-CRT or Whole organ	Classic RILD††	Mean dose <30-32	<5	Excluding patients with pre-existing liver disease or hepatocellular carcinoma, as tolerance doses are lower in these patients
	Whole liver – GTV	3D-CRT	Classic RILD	Mean dose <42	<50	
	Whole liver – GTV	3D-CRT or Whole organ	Classic RILD	Mean dose <28	<5	In patients with Child-Pugh A preexisting liver disease or hepatocellular carcinoma, excluding hepatitis B reactivation
	Whole liver – GTV	3D-CRT	Classic RILD	Mean dose <36	<50	as an endpoint
	Whole liver –GTV	SBRT (hypofraction)	Classic RILD	Mean dose <13	<5	3 fractions, for primary liver cancer
				<18	<5	6 fractions, for primary liver cancer
	Whole liver – GTV	SBRT (hypofraction)	Classic RILD	Mean dose <15	<5	3 fractions, for liver metastases
				<20	<5	6 fractions, for liver metastases
	>700 cc of normal liver	SBRT (hypofraction)	Classic RILD	D_{max} <15	<5	Critical volume based, in 3–5 fractions
Kidney	Bilateral whole kidney‡	Bilateral whole organ or 3D-CRT	Clinically relevant renal dysfunction	Mean dose <15–18	<5	
	Bilateral whole kidney‡	Bilateral whole organ	Clinically relevant renal dysfunction	Mean dose <28	<50	
	Bilateral whole kidney‡	3D-CRT	Clinically relevant renal dysfuntction	V12 <55% V20 <32% V23 <30% V28 <20%	<5	For combined kidney
Stomach	Whole organ	Whole organ	Ulceration	D100‖ <45	<7	
Small bowel	Individual small bowel loops	3D-CRT	Grade ≥ 3 acute toxicity§	V15 <120 cc	<10	Volume based on segmentation of the individual loops of bowel, not the entire potential peritoneal space
	Entire potential space within peritoneal cavity	3D-CRT	Grade ≥ 3 acute toxicity§	V45 <195 cc	<10	Volume based on the entire potential space within the peritoneal cavity

(*Continued*)

Table 1. QUANTEC Summary: Approximate Dose/Volume/Outcome Data for Several Organs Following Conventional Fractionation (Unless Otherwise Noted)* (*Continued*)

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Rectum	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V50 <50%	<15 <10	Prostate cancer treatment
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V60 <35%	<15 <10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V65 <25%	<15 <10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V70 <20%	<15 <10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V75 <15%	<15 <10	
Bladder	Whole organ	3D-CRT	Grade ≥ 3 late RTOG	Dmax <65	<6	Bladder cancer treatment. Variations in bladder size/shape/location during RT hamper ability to generate accurate data
	Whole organ	3D-CRT	Grade ≥3 late RTOG	V65 ≤50 % V70 ≤35 % V75 ≤25 % V80 ≤15 %		Prostate cancer treatment Based on current RTOG 0415 recommendation
Penile bulb	Whole organ	3D-CRT	Severe erectile dysfunction	Mean dose to 95% of gland <50	<35	
	Whole organ	3D-CRT	Severe erectile dysfunction	D90‖ <50	<35	
	Whole organ	3D-CRT	Severe erectile dysfunction	D60-70 <70	<55	

Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy, SRS = stereotactic radiosurgery, BED = Biologically effective dose, SBRT = stereotactic body radiotherapy, RILD = radiation-induced liver disease, RTOG = Radiation Therapy Oncology Group.

* All data are estimated from the literature summarized in the QUANTEC reviews unless otherwise noted. Clinically, these data should be applied with caution. Clinicians are strongly advised to use the individual QUANTEC articles to check the applicability of these limits to the clinical situation at hand. They largely do not reflect modern IMRT.

† All at standard fractionation (*i.e.*, 1.8–2.0 Gy per daily fraction) unless otherwise noted. Vx is the volume of the organ receiving ≥ x Gy. Dmax = Maximum radiation dose.

‡ Non-TBI.

§ With combined chemotherapy.

‖ Dx = minimum dose received by the "hottest" x% (or x cc's) of the organ.

¶ Severe xerostomia is related to additional factors including the doses to the submandibular glands.

** Estimated by Dr. Eisbruch.

†† Classic Radiation induced liver disease (RILD) involves anicteric hepatomegaly and ascites, typically occurring between 2 weeks and 3 months after therapy. Classic RILD also involves elevated alkaline phosphatase (more than twice the upper limit of normal or baseline value).

‡‡ For optic nerve, the cases of neuropathy in the 55 to 60 Gy range received ≈59 Gy (see optic nerve paper for details). Excludes patients with pituitary tumors where the tolerance may be reduced.