Structure of the organ site-specific papers – QUANTEC-2 Template

Structure of the QUANTEC 2 site-specific papers will closely follow the structure used in HyTEC publications. Specifically, papers will contain 10 subsections:

1. Clinical Significance.
2. Endpoints.
3. Challenges Defining and Segmenting Anatomic Volumes.
4. Review of Outcomes Data.
5. Factors Affecting Outcomes.
6. Mathematical and Biological Models.
7. Special Situations.
8. Evidence-Based Dose-Volume Objectives.
9. Future Studies.
10. Reporting Standards.

QUANTEC 2 reports are intended to be self-contained. Therefore, sections 1-3 will in part replicate the narrative used in the original QUANTEC and HyTEC publications.

Section 1: Clinical Significance.

- This section broadly introduces the Organ(s) at Risk (OAR) for radiotherapy-associated effects. Authors may opt to discuss relevant clinical trials and current approaches – such as routine use of image guidance - to minimize risks of adverse events.
- Interactions between RT-associated effects to different organs can be noted here as well (e.g., shortness of breath can be caused by effects on the lungs +/- heart +/- bone marrow).

Section 2: Endpoints.

This section describes clinically reported complications after radiotherapy. As noted, for those OARs reviewed in QUANTEC and/or HyTEC, redundancy with those previous publications is unavoidable as it is optimal for each paper to give a comprehensive overview of the existing evidence and literature and to be read and understood without need to link to another or prior publications. With respect to the specific aims of QUANTEC-2, consider presenting the following:

- Observed acute and late effects.

    - Description of the most impactful endpoints
- Objective scoring systems used in clinics and clinical trials. Figure 1 shows a representative example.
- Use of advanced imaging to assess or confirm treatment-related complications
    - If applicable, objective imaging-based scores

Might also consider the following, if applicable:

SOMA structure (Green J, Vol 25, Issue 1 - 1995 and Red J, Vol 31, Issue 5 - 1995) of

- Subjective symptoms
- Objective signs
- Management (interventions)
- Analytic (labs, imaging)

- Focal vs Global effects
- Symptomatic vs Asymptomatic effects (examples below)

LUNGS	**Focal**	**Global**
Asymptomatic	Fibrosis on CT; reduced SPECT perfusion	Decline in PFTs
Symptomatic	Hemoptysis	Shortness of breath

HEART	**Focal**	**Global**
Asymptomatic	Reduced perfusion on SPECT	Decline in ejection fraction
Symptomatic		Shortness of breath

Section 3: Challenges Defining and Segmenting Anatomic Volumes.

As noted, overlaps with previous publications are unavoidable. With respect to the specific aims of QUANTEC-2, consider presenting the following:

- Summary of newer/consensus OAR contouring guidelines including advice to guide clinical practice (particularly any not described in prior QUANTEC , PENTEC or HyTEC papers)
- Use of multi-modality imaging to aid in OAR delineation.
- Substructure contouring, as this connects to endpoints. For example, inferior, middle and superior pharynx rather than pharynx as whole; white matter tracts in the brain; heart chambers and heart substructures (for example left anterior descending artery).

- Auto-contouring, including of substructures. Specify if auto-contouring (templates, semi-automated, AI-guided tools) is routinely used to delineate specific OARs. Specify what quality assurance procedures are used to assess the fidelity of these auto contours, if any.

We recommend the authors discuss and advocate for following either AAPM 263, ASTRO, and/or the RT Trials Global Harmonization Group (GHG) nomenclature.

Sections 4-6 describe the data used to inform recommended dose-volume objectives and are briefly summarized below.

Further guidance on how to perform the systematic review and what to specifically include in sections 4-6 is pending. Therefore, please do not start this formal review yet. We will be back in touch with specifics on the methodology and details of sections 4-6 in August or September 2026. The Greyed out text serves as a preliminary draft.

Section 4: Review of Outcomes data.

- Specific components of systematic review must be fulfilled. Guidelines based on PRISMA (metanalysis) and TRIPOD (modeling robustness) along with a tutorial for the literature search, literature review, and objective assessment of studies will be provided separately.
- Use section 4 to briefly describe the review process. It is recommended that a checklist (databases, search terms, inclusion/exclusion criteria, etc) is included as supplementary material, an example of a checklist will be provided in literature review guidelines.

Cut-points, in D_x and V_x style, are reported in this section. Other dosimetric values may also be relevant (such as mean dose, maximum dose). When reporting these cut-points consider including the following:

- Report dosimetric correlates showing statistically significant associations with complication risks as well as cut-points explored in particular papers. Consider generating a supplementary material table showing detailed summaries including explored and significant cut-points. This section can be subdivided, e.g., to show data for patients diagnosed with different tumor types.
- Authors can choose to compare outcomes for 3DCRT vs IMRT/VMAT if there exist sufficient data to justify a comparison. Consider making a statement specifying circumstances under which use of a particular technology will benefit patients.

- Where applicable, authors may choose to separately report cut-points for conventional fractionation, moderate hypofractionation (i.e., ~2.3-4Gy) and ultrahypofractionation (i.e., doses typically used for SRS, SBRT and SABR).
- Authors may choose to compare outcomes for photon-based vs proton-based therapy if there exist sufficient data to justify a comparison.
- If published data describe different dose/volume/outcome relationships based on specific clinical factors, then that specific data should be summarized in Section 4, perhaps by reporting these relationships in the different patient subgroups. Clinical factors include the following:
    - prior resection
    - systemic therapy
    - comorbid conditions
    - environmental or substance exposures

  If the impact of these clinical factors are not directly linked to dose/volume/outcome data, then these clinical factors should be discussed in Sections 5 (Factors affecting outcomes) and 7 (Special situations, to report accounting for modulating factors).
- Consider summarizing the data in graphical form. Figures 2 and 3 show representative examples.

Section 5: Factors Affecting Outcomes.

This section describes clinical risk factors for the endpoints that are discussed in the report. Those clinical factors that have enough data to be analyzed quantitatively by NTCP modelling should be discussed in sections 4 and 6 (and perhaps briefly mentioned here). This section is intended for qualitative/descriptive summaries and/or quantitative results that do not lend themselves to NTCP modelling.

The following are specific examples of clinical factors that might be included in the report:

- Pre-existing conditions, including:
    - Genetic conditions, e.g. those that confer radiosensitive
    - Baseline conditions that impact organ functionality
    - Presence of-comorbidities
    - Sub-clinical/pre-clinical aspects captured by imaging and/or other biomarkers (as an example: blood sample)
- Personal habits, e.g., tobacco use; alcohol use
- Occupational exposures e.g. asbestos, silica, aniline dyes, etc.
- Prior or subsequent non-radiotherapy local treatments (such as surgery)

- Prior, concurrent or subsequent systemic treatments therapies [especially newer therapies that were not used in the QUANTEC 1 era]
- Tumor size/location
- Other biologic correlates and biomarkers
- Other factors specific to OAR. Examples include:
    - Lung: risks after prior pneumonectomy, such as mesothelioma?
    - Heart: transplanted heart, or patients with implanted devices (Watchman, AICDs, pacemakers)
    - Bone (implanted, hip replacements)
    - Kidney: patients with one kidney, or with a transplanted kidney

Section 6: Mathematical and Biologic Models.

This section is what makes QUANTEC-2 unique and impactful. This section summarizes the QUANTEC dose-response or dose-volume-response models that are based upon data extracted from published papers.

These models may be reported in various manners, from incidence of complications analyzed as a function of a DVH cut-point value, for example V_{20Gy} for lung injury, to full dose-volume-response, for example Lyman-Kutcher-Burman (LKB) (LKB) model including obtained values for D_{50}, n, and m model parameters. When reporting these models, consider including the following.

- A brief description of the data set
- Dose conversion if applicable, e.g., reported as physical dose or EQD2
- Model used (e.g. mechanistic, phenomenological, data-driven (logistic/Cox regression), machine learning (clustering, traditional deep learning))
- If applicable, clinically informed projections for what is considered acceptable risk of complications

Consider presenting the NTCP data and dose-response curves as graphs (see figure 4 as a representative example), and model parameters (see figure 5).

A comparison vs the original QUANTEC models, if applicable, is appropriate.

Also, consider summarizing the following, if data are sufficient and question is clinically relevant:

- Do models/model predictions based on 3DCTR vs IMRT/VMAT agree?

- Do models/model predictions based on conventional, hypo- or ultra-hypo fractionation agree?
- Do models describing dose-response or dose-volume-response following proton RT agree with those based on photon RT data (RBE effect)?
- Do models account for confounding factors affecting outcomes? Figure 6 shows a representative example.

Section 7: Special Situations.

This section is intended to report how risk is impacted by unique factors not covered in Section 5. As with Section 5, these factors should include those where there are not enough data to separately model risks, or where it would be outside the scope of this report to do so (as may be the case with reirradiation or pediatrics). This section will likely be the most variable across organs, since these "special situations" will vary by OAR.

The following are specific examples of clinical factors that might be included in the report:

- Pediatric vs AYA vs adult populations - it is anticipated that this would be descriptive as opposed to quantitative, given the recent publication of PENTEC reports
- Dose per fraction and scheduling effects, e.g., hypo- vs hyperfractionation, shorter vs. longer treatment times, BID vs QD vs. weekly
- In-field boosts/dose-painting
- Re-irradiation – it is anticipated that this would be descriptive (i.e., prior radiation is reported to increase risks of *complication* XX-YY-fold), since separate efforts are specifically addressing NTCP in the setting of re-irradiation
- Any other situation that is unique or special and not covered in Section 5.

If clinically relevant, this section can be used to review and report complications not commonly reported.

Section 8: Evidence-Based Dose-Volume Objectives.

This section summarizes dosimetric thresholds that can be considered to guide plan optimization, based on calculated complication probabilities risks. Dose-volume objectives should be presented as they relate to observed complication risks. We are aiming to avoid terminology such as "recommend" or "recommendations" and emphasize that the report aims to quantify risks. For example, rather than stating : "To minimize the risk of *complication* the following D_x constraints are recommended…", consider stating "Our NTCP analysis shows that the following D_x limits, would likely result in risks of <Y%. Further reduction of D_x to … decreases the risk to <Z%."

Section 9: Future Studies.

This section identifies gaps in knowledge and emerging studies/technologies. Ideally, authors would prioritize what is most important to realistically investigate (as opposed to a long, idealistic laundry list).

Section 10: Reporting Standards.

This section has to provide minimum sufficiency and a comprehensive list of items that are required in publications. This applies to all aspects, from patient selection to treatment planning/delivery, planning data acquisition, and follow-up. Authors can prioritize what is most needed, among a comprehensive 'ideal' dataset, to facilitate pooling data.

Table 1 Scoring systems for optic nerve and optic chiasm toxicity

Scoring system	Criteria
RTOG/EORTC LENT SOMA subjective (vision)	
Grade 0	None
Grade 1	Indistinct color vision
Grade 2	Blurred vision, loss of color vision
Grade 3	Severe loss of vision, symptomatic visual field defect with decrease in central vision, some ability to perform ADL
Grade 4	Blind, inability to perform ADL
RTOG/EORTC LENT SOMA objective (optic nerve)	
Grade 0	None
Grade 1	Afferent pupillary defect with normal-appearing nerve
Grade 2	<1/4 pallor with asymptomatic visual field defect
Grade 3	>1/4 pallor or central scotoma
Grade 4	Profound optic atrophy, complete blindness
CTCAE version 3 (cranial nerve II neuropathy)	
Grade 0	None
Grade 1	Asymptomatic, detected on examination/testing only
Grade 2	Symptomatic, not interfering with ADL
Grade 3	Symptomatic, interfering with ADL
Grade 4	Life-threatening; disabling
CTCAE version 4 (optic nerve disorder)	
Grade 0	None
Grade 1	Asymptomatic; clinical or diagnostic observations only
Grade 2	Limiting vision of the affected eye (20/40 or better)
Grade 3	Limiting vision in the affected eye (worse than 20/40 but better than 20/200)
Grade 4	Blindness (20/200 or worse) in the affected eye*

Abbreviations: ADL = activities of daily living; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organization for Research and Treatment of Cancer; LENT = Late Effects in Normal Tissue; RTOG = Radiation Therapy Oncology Group; SOMA = Subjective, Objective, Management, Analytic.

* Proposed for version 5: Best corrected visual acuity of 20/200 or worse in the affected eye.

Figure 1: A representative example showing scoring systems.

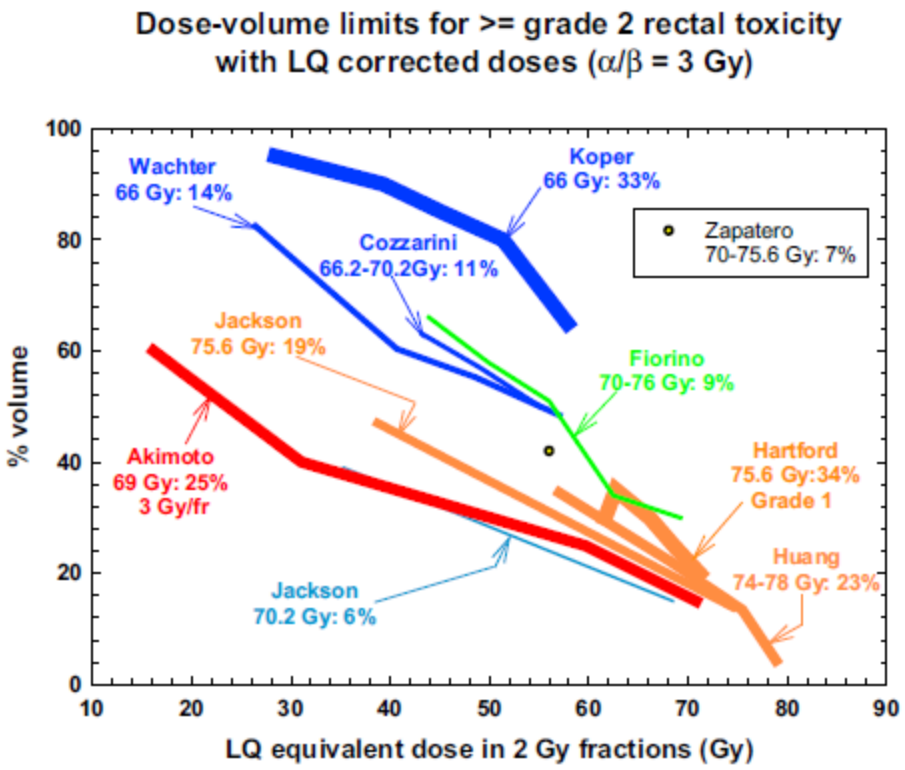


Figure 2: A representative example of a figure summarizing D_x and V_x cut-points for rectal complications.

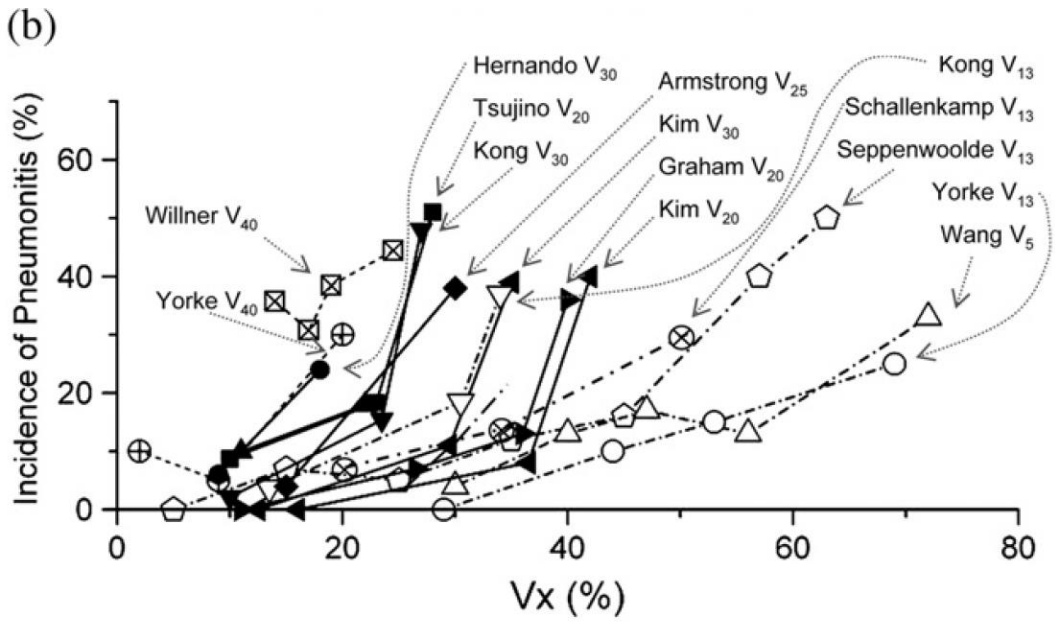
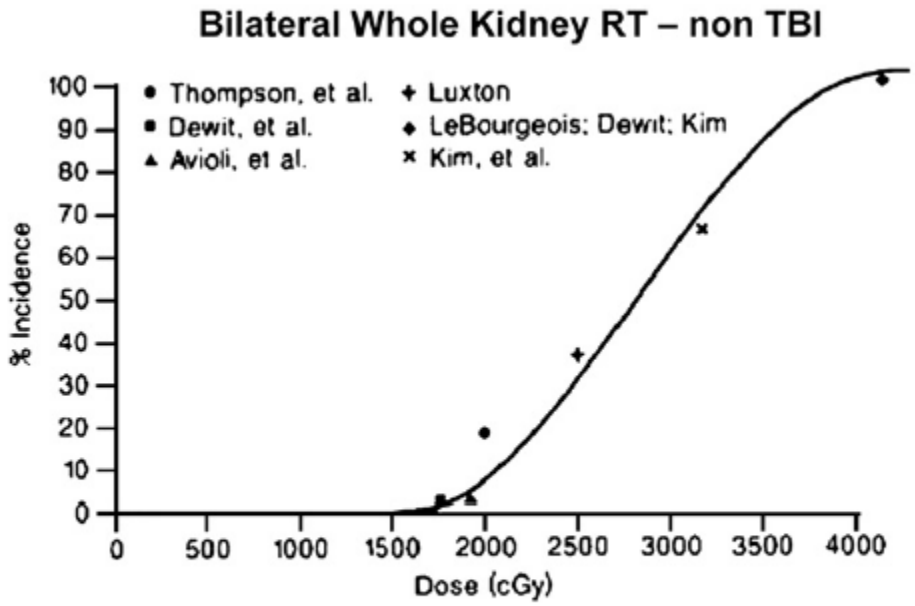


Figure 3: A representative example of a figure summarizing V_x cut-points for incidence of pneumonitis.



Dose–response curve for symptomatic kidney injury after non–total body irradiation of bilateral kidneys. Note, y axis is different from than that in Fig. 1. Data from review from Cassady *et al.* (10).

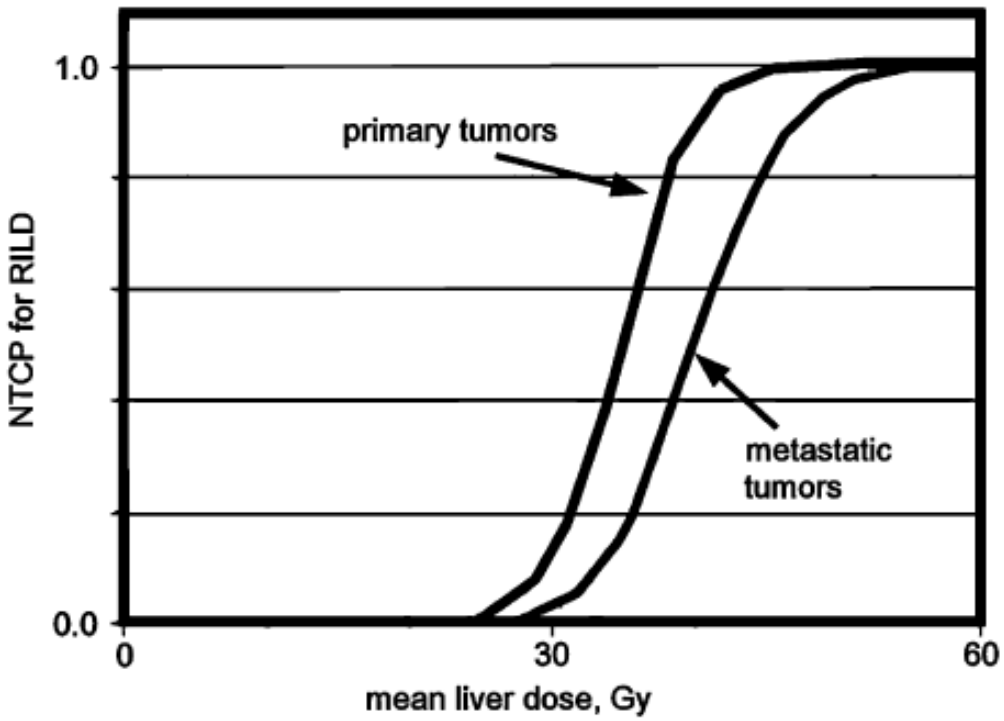
Figure 4: A representative example of a figure showing dose-response data and the model.

Table 1. Larynx edema: estimated parameter values for various NTCP models with their 1D-68% confidence intervals

Model			*n*
LKB	D50	m	
Rancati *et al.* (10)	46.3 Gy	0.16	0.45
SD	1.8 Gy	0.05	0.28
LOGEUD	D50	k	
Rancati *et al.* (10)	46.0 Gy	9.95	0.47
SD	1.85 Gy	3.46	0.3

Abbreviations: NTCP = normal tissue complication probability; LKB = Lyman-Kurcher-Burman; D50 = dose causing 50% risk of complications; LOGEUD = log equivalent uniform dose.

Figure 5: Summary of model parameters.



Mean liver dose, corrected with LQ modeling for 2.0 Gy fractions vs. Lyman normal tissue complication probability (NTCP) of classic radiation-induced liver disease (RILD) for primary and metastatic liver cancer, redrawn from (24).

Figure 6: Dose-response models showing radiation-induced liver disease as a function of mean liver dose, with models produced separately for primary and metastatic tumors.