Table 2 Summary of NTCP[6] estimates after SRS/SBRT from the HyTEC reports*

Organ	Volume segmented	Number of fractions	Endpoint	Dose (Gy) or dose-volume parameters	Rate (%)*	Notes
Brain; for metastasis	Total brain including target	1	Symptomatic necrosis	$V_{12Gy} \leq 5$ cm^3	10%	From Table 3 and Figs. 4 and 5 in paper.
		1	Symptomatic necrosis	$V_{12Gy} \leq 10$ cm^3	15%	Consistent with QUANTEC.
		1	Symptomatic necrosis	$V_{12Gy} \leq 15$ cm^3	20%	Prior whole brain RT appears to not markedly increase risks in most reports (with the exception of brain stem).† However, repeat SRS/fSRS to the same area has been associated with markedly increased risks.
		3	Edema or necrosis	$V_{20Gy} \leq 20$ cm^3	$\leq 10\%$	
		3	Edema or necrosis	$V_{20Gy} \leq 30$ cm^3	$\leq 20\%$	
		5	Edema or necrosis	$V_{24Gy} \leq 20$ cm^3	$\leq 10\%$	
		5	Edema or necrosis	$V_{24Gy} \leq 30$ cm^3	$\leq 20\%$	
Brain; SRS for arteriovenous malformation	Total brain including target	1	Symptomatic necrosis	$V_{12Gy} \leq 10$ cm^3	$\leq 10\%$	From Figure 2 in paper
Optic pathway	Optic nerves and chiasm	1	Neuropathy	$D_{max} < 10$-12 Gy	$< 1\%$	From Table 3 in paper. Consistent with QUANTEC. Prior RT exposure of the optic pathway (either whole brain RT or SRS/fSRS) appears to markedly increase risks.
		3	Neuropathy	$D_{max} < 20$ Gy	$< 1\%$	
		5	Neuropathy	$D_{max} < 25$ Gy	$< 1\%$	
Carotid artery (re-treatment)	Each carotid artery	5	Grade 3-5 bleeding	$D_{max} < 20$-30 Gy	< 2-12%	Dose-volume metric shown is for the reirradiation SBRT dose *in patients with prior RT*‡
	Each carotid artery	5	Grade 3-5 bleeding	$D_{0.5cc} < 20$ Gy	< 2-12%	Dose-volume metric shown is for the reirradiation SBRT dose *in patients with prior RT*‡
Lungs	Combined lungs minus target§	3-5	Grade ≥ 2 toxicity§	Mean dose ≤ 8 Gy; $V_{20Gy} < 10$-15%	10-15%	Preexisting interstitial lung disease appears to increase toxicity risk
Liver; SBRT for primary lesions	Liver minus GTVs‖	3	Grade ≥ 3 liver enzyme change	Mean dose ≤ 13 Gy	<20%	For patients with intact liver function. Various clinical factors (eg, underlying liver impairment per the Child Pugh score, platelet count) can reduce liver tolerance.# Consistent with QUANTEC (that broadly considered radiation induced liver injury; this includes liver enzyme changes).
	Liver minus GTVs‖	6	Grade ≥ 3 liver enzyme change	Mean dose ≤ 18 Gy	<20%	
Liver; SBRT for metastases	Liver minus GTVs‖	3	Grade ≥ 3 liver enzyme change	Mean dose ≤ 15 Gy	<20%	
	Liver minus GTVs‖	6	Grade ≥ 3 liver enzyme change	Mean dose ≤ 20 Gy	<20%	

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Table 2 (*continued*)

Organ	Volume segmented	Number of fractions	Endpoint	Dose (Gy) or dose-volume parameters	Rate (%)*	Notes
Liver; SBRT for metastases	Liver minus GTVs‖	3-6	Liver dysfunction and grade 3-5 general GI toxicity¶	≥700 cm^3 receives ≤ 15-17 Gy#	<13%	Critical volume limit, spare 700 cm^3**
Bladder	Bladder (as a solid organ)††	4-5	Late grade ≥2 urinary toxicity	$V_{Prescription\ Dose}$ < 5-10 cm^3	<20%	In context of prostate SBRT. All reviewed prescription doses were 35-40 Gy in 4-5 fractions. See Pelvic NTCP paper, Table 4, for additional constraints. Many of the reviewed studies treated every-other-day in hopes of reducing toxicity.
Rectum	Rectum (as a solid organ)††	4-5	Late grade ≥3 bowel toxicity	D_{max} < 35-38 Gy	<3%	
Urethra	Prostatic urethra	4-5	Late grade ≥2 urinary toxicity	D_{max} < 38-42 Gy	<20%	
Spinal cord	Spinal cord, canal, or thecal sac‡‡	1 2 3 4 5	Myelopathy	D_{max} < 12.4-14 Gy D_{max} < 17-19.3 Gy D_{max} < 20.3-23.1 Gy D_{max} < 23-26.2 Gy D_{max} < 25.3-28.8 Gy	1-5% 1-5% 1-5% 1-5% 1-5%	These data are for patients without prior RT (from Table 3 in paper). Information for the setting of re-irradiation are in Table 4 of the paper. Consistent with QUANTEC.

Abbreviations: CTV = clinical target volume; D_{max} = maximum dose; GI = gastrointestinal; GTV = gross target volume; HyTEC = Hy Dose per Fraction, Hypofractionated Treatment Effects in the **C**linic; NTCP = normal tissue complication probability; PTV = planning target volume; QUANTEC = Quantitative Analyses of Normal Tissue Effects in the Clinic; RT = radiation therapy; SBRT = stereotactic body radiation therapy; SRS = stereotactic radiosurgery.

* Although the source data may have included some patients who had undergone reirradiation (refer to the individual reports for specifics), unless stated otherwise, the NTCP risks from the compiled data are meant to apply for patients who received no prior radiotherapy. Acceptable risk in any given patient should reflect the clinical decision making of the physician and consent of the patient. Providers are strongly advised to use the individual HyTEC articles to assess the full context and applicability of these values for each scenario. Because the overall survival duration is limited in many patients who receive SRS/SBRT, the long-term NTCP may not be accurately represented by the reported data. There are several other reference documents that address these and other sites (eg, *Seminars in Radiation Oncology*[37,38]).

† Prior whole brain RT appears to increase risk of subsequent SRS/fSRS to the brain stem (see brain stem subsection in special situations section of the paper).

‡ Nominal prior prescription of 200 cGy × 35 fractions = 7000 cGy. Major risk factors include: circumferential irradiation of carotid or other major vessel; skin invasion by cancer; necrosis or infection at site; surgical manipulation of site before, and <6 month interval since prior RT.

§ Most studies appear to have excluded the target volume (eg, GTV, CTV, or PTV) from the calculation of lung dose-volume parameters (see Tables 3 and E1 in paper). Variable grading scales used.

‖ Evaluation structure in most reviewed papers for liver enzyme changes is liver minus GTV.

¶ GI toxicity includes: fatigue, nausea, diarrhea, gastritis, ulcers, GI area pain, colitis.

Since this analysis was completed, there have been additional studies relating dose-volume metrics to clinically relevant endpoints that were not included in this work (eg, decline in synthetic liver function). Dose metrics (eg, mean dose or D 800 cm^3, maximum dose to the coldest 800 cm^3) have been associated with these endpoints; (eg, see Velec et al[39] and Pursley et al[40]).

** In patients with hepatocellular cancer, sparing ≥800 cm^3 to ≤18 Gy in 3 fractions has been suggested (Son et al[41]).

†† Solid organ refers to the entire volume included within the external wall (as opposed to the approach some have taken to consider only the wall of these organs; that is, excluding the contents).

‡‡ A range of doses and complication rates are reported, reflecting the heterogeneity and uncertainty in the data. The spinal cord, canal, and the thecal sac have each been used in different models of radiation myelopathy.

A summary of the key dose, volume, and outcome data for the organs and tumors considered in HyTEC is provided in Tables 2 and 3. In generating the table entries, preference was given to providing published clinical data when available. Thus, for situations where both clinical and model-based data were available, the clinical data were favored. Further, the NTCP data shown are largely for patients who have received no prior radiation therapy (RT), and the entries reflecting situations with prior RT are so noted. We recognize and emphasize that the data are imperfect. For many tumor sites, local recurrence is difficult to establish with certainty by noninvasive imaging

Table 3 Summary of TCP estimates from the HyTEC reports*

Tumor site/type	Volume segmented, margin	Number of fractions	Endpoint†	Dose (Gy), or dose-volume parameters‡	Rate (%)†	Notes
Brain metastases	GTV + 0-2 mm margin§	1	2-year local control,	≤2 cm, 18-24 Gy	80%-95%	1-year local control ≈ ≥85%-90%
		1	by lesion size	2-3 cm, 18 Gy	66%	1-year local control ≈ 75%
		1		>3 cm, 15 Gy	47%	1-year local control ≈ 70%
		3		2-3 cm, 24-30 Gy	65%-84%	1-year local control ≈ 80%
		3		>3 cm, 21-27 Gy	53%-69%	1-year local control ≈ 75%
		5		2-3 cm, 30-35 Gy	75%-85%	1-year local control ≈ 80%
		5		>3 cm, 25-30 Gy	59%-69%	1-year local control ≈ 75%
Vestibular Schwannoma	GTV+ 0-2 mm margin‖	1	3-5 year local control	≥12 Gy	≥91%	Variable PTV margins used. Most available data are with a single fraction.
		3		18 Gy	≥91%	
		5		25 Gy	≥91%	
Head & neck; retreatment	GTV + 0-6 mm margin	5	2-year local control	45 Gy	50%	Majority of newer studies used 2-6 mm margin
Lung; T1-2 lesions¶	ITV or IGTV + 3-8 mm	3	1-5 year local control	33 Gy	<50%	Based on minimal data
		3	1-5 year local control	45-54 Gy	≥75%	In most studies
		3	1-5 year local control	≥60 Gy	≥80%-85%	In most studies
		4	1-5 year local control	42-48 Gy	≥70%	In most studies
		4	1-5 year local control	>52 Gy	≥80%-85%	In most studies
		5	1-3 year local control	≥ 50 Gy	≥ ≈ 80%	In all studies
Liver; primary tumor	Variable	3-5	2-year local control	BED_{10} = 60-72 Gy#	90%	No clear dose response relationship within the range of reported schedules (including 11-18 Gy x 3; 12 Gy x 4; 8-10 Gy x 5). Authors recommend 8-10 Gy x 5 as a conservative approach.
Liver metastases	Variable	1-5	2-year local control	BED_{10} > 100 Gy#	≥90%	Estimated based on BED_{10} >112, including 15-25 Gy x 3
		1-5		BED_{10} < 100 Gy#	65%-76%	Estimated based on BED_{10} ranging from 60-84 Gy, including 24-26 Gy x 1; 10-12.5 Gy x 3; 10 Gy x 4
Adrenal	Mixed**	Median 5††	1-year local control	Prescription BED_{10} > 116.4 Gy	>95%	Model-based estimate. Clinical examples of fractionation schedules providing BEDs in this range include 15 Gy x 3 = 45 Gy (BED_{10} = 112.5) and 11 Gy x 5 = 55 Gy (BED_{10} = 115.5 Gy). Respiratory motion control in all studies.

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Table 3 (*continued*)

Tumor site/type	Volume segmented, margin	Number of fractions	Endpoint[†]	Dose (Gy), or dose-volume parameters[‡]	Rate (%)[†]	Notes
Pancreas	GTV + 2-5 mm	1 3 5	1-year local control	20-25 Gy 30-36 Gy 33 Gy	79%-88% 79%-86% 77%	Rates shown are without surgery (reported local control rates are higher in patients with surgery pre- or post-SBRT)
Prostate, low-intermediate risk	Varied: prostate + 0-5 mm PTV margin	5	5-year freedom from biochemical relapse	36.1 Gy[‡‡]	95%	
Prostate, high risk		5		38.7 Gy[‡‡]	95%	Caution is needed in interpreting these data because few such patients are included in the published literature and these are likely highly selected patients.
Spine[§§]	CTV + 0-2 mm	1 1 1 1 2 3 3	2-year local control	18 Gy 20 Gy 22 Gy 24 Gy 24 Gy 27 Gy 30 Gy	82% 90% 94% 96% 82% 78% 85%	Much uncertainty exists in interpreting the data from the literature and in the creation of these resultant model based estimates.

Abbreviations: GTV = gross target volume; HyTEC = Hy Dose per Fraction, Hypofractionated Treatment Effects in the Clinic; PTV = planning target volume; SBRT = stereotactic body radiation therapy; TCP = tumor control probability.

* The control probability in any given individual cannot be accurately quantified. Acceptable goals in any given patient should reflect the clinical decision making of the physician and consent of the patient. Providers are strongly advised to use the individual HyTEC articles to assess the full context and applicability of these values for each scenario. There are several other reference documents that address these and other issues (eg, *Seminars in Radiation Oncology*[37,38]).

† Some reports estimate local control via an actuarial method. Care is needed when interpreting actuarial data in the setting of metastatic cancer. Often, the local control is estimated by censoring patients at the time of death, and the accuracy of actuarial techniques requires that censoring events should be independent of the endpoint under consideration. Because the pace of disease beyond the treated site (that can cause the censoring event of death) and the pace of regrowth of treated site (that obviously impacts local recurrence) are likely related, actuarial estimates may not be accurate and may overstate the local control. (Gelman[42]). Similarly, for many tumor sites, local recurrence is difficult to establish with certainty by noninvasive imaging methods, and there are other statistical issues (eg, a failure to consistently assess for local failure in patients with systemic disease, and favorable patient selection for both retrospective analyses and prospective studies) that collectively may tend to overestimate the true local control rates across an entire population.

‡ BED, biological effective dose, calculated per linear quadratic model = total dose × (1 + (dose per fraction) / (α/β)) BED_{10} = BED calculated with an α/β value of 10.

§ Brain: GTV to PTV expansion range was 0-3 mm, but most people use 0-2 mm given concern for increased radionecrosis with larger expansions. The median expansion in the reviewed studies was 1 mm.

‖ Vestibular Schwannoma: Only 29% of manuscripts reported the use of a PTV margin of 1 or 2 mm; therefore, for most data, GTV was assumed to be the same as PTV.

¶ Lung: Planning generally with 3D rather than intensity modulated radiation therapy (IMRT). Doses listed are to the PTV. Since this analysis was completed, there have been additional models suggested (eg, Jeong et al[43]).

This paper used the notation Gy_{10} rather than BED_{10} as is used in other HyTEC papers, but they are mathematically the same.

** Adrenal: Targets were mixed: GTV, ITV, or PTV. PTV is usually GTV or ITV +3-10 mm; usually there is no margin for CTV.

†† Adrenal median over all studies = 5 (range, 1-27).

‡‡ Prostate: Many series use heterogeneous planning, intentionally including hot spots within the much of the prostate. The average prescription isodose line reported among studies used in the manuscript was 85%, and most of those had prescription isodose lines of 70%-90%. The prescription isodose line for heterogeneous planning may run as low as 50%, to more specifically mimic the intraprostatic dose escalation morphology characteristics of HDR brachytherapy.

§§ Spine: A minimum dose to the tumor (D_{min}) of greater than 14-15 Gy in a single fraction equivalent or a GTV D95 of greater than 18.3 Gy in 1 fraction may correlate with tumor control to a greater degree than the prescribed dose. Thus, if able, care should be taken to minimize under-dosage of the target tissues. Please see section 8 of the paper for a deeper discussion of this issue.

methods, and there are statistical issues (eg, competing risks, a failure to consistently assess for local failure in patients with systemic disease, and favorable patient selection for both retrospective analyses and prospective studies) that collectively may tend to overestimate the true local control rates across an entire population.