

## Supplementary Material

**Table S1.** Specific dose-volume constraints for Emerging OARs.

Organ	Imaging Technique	Constraints (Conventional Fractionation)* (3)
Aorta		$D_{MAX(1\text{ cm}^3)} < 74\text{ Gy}$ [99] [C]
Bichat Fat Pad		No organ Volume reduction with Dmax 70 Gy [100] [D]
Bone Marrow		BM- $V_{10\text{Gy}} < 90\%$ [68] [C]; BM- $V_{20\text{Gy}} < 84\%$ [101] [C]; BM- $D_{MEAN} < 25\text{ Gy}$ (optimal); BM- $D_{MEAN} < 30\text{ Gy}$ (mandatory) [102][C]; LSS- $V_{10\text{Gy}} < 85\%$ ; LSS- $D_{MEAN} < 28\text{ Gy}$ [102] [C]; LSS- $V_{15\text{Gy}} < 85\%$ [101] [C]
Femur		$D_{MAX} < 60\text{ Gy}$ mandatory $D_{MAX} < 50\text{ Gy}$ optimal [103,104] [C]
Hypothalamus	T1-weighted MRI	$D_{MAX} < 50\text{ Gy}$ [105] [C]
Temporo-mandibular -joint		$D_{MAX(0.1\text{ cm}^3)} < 70\text{ Gy}$ [35] [A]
Vagina		$D_{2\text{cm}^3} \leq 145\text{ Gy EQD2 (EBRT+BRT)}$ [106] [C] $D_{\text{rectovaginalpoint}} \leq 65\text{ Gy EQD2 (EBRT+BRT)}$ [107] [C] †

**Legend:** BM: Bone marrow; BRT brachytherapy; DMax: Maximum Dose; DMean: Mean Dose; EBRT: External Beam Radiation Therapy, EQD2: Equivalent dose in 2-Gy fractions; Gy: Gray; LSS: Lumbosacral Spine; OAR: Organ at Risk; The anatomical descriptions are reported in Table 2. Common abbreviations were used in the tables:  $V_{\odot}$  = Volume receiving a dose  $\geq \odot$  Gy,  $D_{\odot\odot}$  = dose received by % of the organ volume,  $D_{\odot}$  = dose received by  $\gamma$  cm<sup>3</sup> (the cubic centimeters) of the organ volume, DMAX = maximum dose received by the organ, DMEAN = mean dose received by the organ. Volumes and doses were expressed as percentage (%) or absolute values (cm<sup>3</sup> or Gy, respectively). The letters in square brackets indicate the levels of evidence, classified as follows: [A] International guidelines; [B] literature review on clinical or planning studies; [C] Data from results of clinical or planning studies; [D] expert opinions or used in prospective trials. \*considered 180-200 cGy/fraction, as defined by Marks et al (3); †Dose to the recto-vaginal point, defined in the referred text. [106].

**Table S2.** Specific dose-volume constraints for adult patients treated with curative radiotherapy for Hodgkin Lymphoma.

<b>Organ</b>	<b>Constraints (conventional fractionation) (3)</b>
Aortic valve	$D_{MAX} < 25 \text{ Gy}$ [11] [A]
Bone Marrow	$V_{5Gy}$ : ALARA; $V_{10Gy} < 50\%$ ; $V_{25Gy} < 25\%$ [11] [A]
Bowel Small	$D_{MAX} < 45Gy$ ; $V_{15Gy} < 120 \text{ cm}^3$ [11] [A]
Breast	$D_{MEAN} < 4$ (optimal) ; $D_{MEAN} < 4-15 \text{ Gy}$ (acceptable); $V_{4Gy} < 10\%$ (optimal); $V_{4Gy} : 10\%-20\%$ (acceptable); $V_{10Gy} < 10\%$ (acceptable) [108] [A]
Coronary vessels	Avoid hotspots [11] [A]
Heart	$D_{MEAN} < 8 \text{ Gy}$ (recommended) ; $D_{MEAN} < 15 \text{ Gy}$ (acceptable) [11] [A];
Kidney	$D_{MEAN} < 8 \text{ Gy}$ ; $V_{10Gy} < 30\%$ ; $V_{20Gy} < 15\%$ (recommended) ; $V_{20Gy} < 25\%$ (acceptable) [11] [A]
Lacrimal Gland	$V_{20Gy} < 80\%$ [11] [A]
Left ventricle	$D_{MEAN} < 8 \text{ Gy}$ (recommended) ; $D_{MEAN} < 15 \text{ Gy}$ (acceptable) [11] [A];
Liver	$D_{MEAN} < 15 \text{ Gy}$ ; $V_{20Gy} < 30\%$ ; $V_{30Gy} < 20\%$ [11] [A]
Lung	$V_{5Gy} < 35\%$ (optimal); $V_{5Gy} : 35\%-45\%$ (acceptable); $V_{20Gy} < 20\%$ (optimal); $V_{20Gy} : 20\%-28\%$ (acceptable); $D_{MEAN} < 8 \text{ Gy}$ (optimal); $D_{MEAN} < 8-12 \text{ Gy}$ (acceptable) [108] [A]
Mitral valve	$D_{MAX} < 25 \text{ Gy}$ [11] [A]
Pancreas	Minimize Volume $> 36 \text{ Gy}$ [11] [A]
Parotid Gland	Ipsilateral: $D_{MEAN} < 11 \text{ Gy}$ (recommended); $D_{MEAN} < 24 \text{ Gy}$ (acceptable); Controlateral: ALARA[11] [A]
Pericardium	$D_{100cm^3} < 5 \text{ Gy}$ [11] [A]
Pharyngeal Constrictors Muscles	$D_{MEAN} < 25 \text{ Gy}$ [11] [A]
Pulmonary valve	$D_{MAX} < 30 \text{ Gy}$ [11] [A];
Oral Cavity	$D_{MEAN} < 11 \text{ Gy}$ [11] [A]
Spleen	$D_{MEAN} < 10 \text{ Gy}$ ; $V_{5Gy} \leq 30\%$ ; $V_{15Gy} \leq 20\%$ [11] [A]

Stomach	$D_{MAX} < 45\text{Gy}$ [11] [A]
Submandibular Gland	Ipsilateral: $D_{MEAN} < 11\text{ Gy}$ (recommended); $D_{MEAN} < 24\text{ Gy}$ (acceptable); Controlateral: ALARA[11] [A]
Thyroid Gland	$V_{25\text{ Gy}} < 63.5\%$ ; Minimize V30 [11] [A]
Tricuspid valve	$D_{MAX} < 30\text{ Gy}$ [11] [A]

**Legend:** A\_LAD: Left Anterior Descending Artery; ALARA: “as low as reasonably achievable”, principle of radiation safety; CxCA: Circumflex Coronary Artery; DMax: Maximum Dose; DMean: Mean Dose; Gy: Gray; LMCA: Left Main Coronary Artery, PDA: Posterior Descending Artery; RCA: Right Coronary Artery. Common abbreviations were used in the tables:  $V_{\odot}$  = Volume receiving a dose  $\geq \odot$  Gy,  $D_{\odot\odot}$  = dose received by % of the organ volume,  $D_{\odot}$  = dose received by  $\gamma$  cm<sup>3</sup> (the cubic centimeters) of the organ volume, DMAX = maximum dose received by the organ, DMEAN = mean dose received by the organ. Volumes and doses were expressed as percentage (%) or absolute values (cm<sup>3</sup> or Gy, respectively). The anatomical descriptions are described in Table 2. The letters in square brackets indicate the levels of evidence, classified as follows: [A] International guidelines; [B] literature review on clinical or planning studies; [C] Data from results of clinical or planning studies; [D] expert opinions or used in prospective trials. \*considered 180-200 cGy/fraction, as defined by Marks et al [3].

**Table S3.** Specific dose-volume constraints for adult patients treated with curative radiotherapy for Breast Cancer.

Organ	Moderate Hypofractionation (40 Gy/15 fx)	Ultra- Hypofractionation (5 Fractions)
Anterior Descend-ing Artery	D <sub>MAX</sub> ( ≤ 20 Gy) [109,110][C]	
Breast	D <sub>MEAN</sub> ALARA; D <sub>MAX</sub> < 3% of the prescribed dose [111] [D] V <sub>5Gy</sub> < 15% [112,113] [D]	Contralateral breast D <sub>MAX</sub> <1 Gy [13] [D] †
Heart	V <sub>40Gy</sub> < 3%; V <sub>18Gy</sub> < 5% [114] [D]; V <sub>10Gy</sub> < 5%; V <sub>2Gy</sub> < 30%; [14] [D]; If DIBH : V <sub>13Gy</sub> < 10%; V <sub>13Gy</sub> < 2% (optimal); D <sub>MEAN</sub> < 3 Gy [115] [D]	V <sub>3Gy</sub> < 10% [13] [D] †; V <sub>1.5Gy</sub> < 30%; V <sub>7Gy</sub> < 5 % [14] [D];
Lung	D <sub>MEAN</sub> <10 Gy; V <sub>20Gy</sub> < 10% [114] [D]; V <sub>12Gy</sub> < 15% [14] [D]; V <sub>25Gy</sub> < 5%; V <sub>17Gy</sub> < 8%; V <sub>8Gy</sub> < 10% D <sub>MEAN</sub> < 6.36 Gy Contralateral lung V <sub>2.5Gy</sub> < 15% [111] [D]; If DIBH : Ipsilateral lung : V <sub>18Gy</sub> <10% (optimal); D <sub>MEAN</sub> <6 Gy (optimal); Contralateral lung : V <sub>2.5Gy</sub> <3% (optimal); D <sub>MEAN</sub> <1 Gy (optimal) [115] [D]	Ipsilateral lung : V <sub>10Gy</sub> <20% [13] [D] †; V <sub>8Gy</sub> <15% [14] [D];  Contralateral lung : V <sub>5Gy</sub> <10% [13] [D] †

**Legend:** ALARA: as low as reasonably achievable; DIBH: Deep inspiration breath hold; D<sub>Max</sub>: Maximum Dose; D<sub>Mean</sub>: Mean Dose; Gy: Gray. Consider the anatomical descriptions reported in Table2. Common abbreviations were used in the tables: V<sub>⊙</sub> = Volume receiving a dose ≥ ⊙ Gy, D<sub>⊙⊙</sub> = dose received by % of the organ volume, D<sub>⊙</sub> = dose received by γ cm<sup>3</sup> (the cubic centimeters) of the organ volume, D<sub>MAX</sub> = maximum dose received by the organ, D<sub>MEAN</sub> = mean dose received by the organ. Volumes and doses were ex-pressed as percentage (%) or absolute values (cm<sup>3</sup> or Gy, respectively). The letters in square brackets indicate the levels of evidence, classified as follows: [A] International guidelines; [B] literature review on clinical or planning studies; [C] Data from results of clinical or planning studies; [D] expert opinions or used in prospective trials. \*anatomical description reported in **Table1**; † only for Partial Breast Irradiation.

**Table S4.** Specific dose-volume constraints for pediatric patients.

Organ	Covetional Fractionation *(3)	Comments
Brain	$D_{MAX} < 58-59 \text{ Gy}$ [17] [B]	5% risk of brain necrosis for doses > 58-59 Gy; 5 % risk of neurocognitive function for doses > 35.7, 29.1, 22.2, 18.1 Gy if irradiated brain volume is 10, 20, 50, 100 %, respectively
Brainstem	$D_{MAX} < 55.8 \text{ Gy-RBE}$ $V_{55\text{Gy}} \leq 6\%$ [116] [C]	
Cochlea	$D_{MEAN} < 35 \text{ Gy}$ [40] [B]	
Hearth	$D_{MEAN} < 15 \text{ Gy}$ [20] [A] $V_{20\text{Gy}} < 0.1 \%$ ; $V_{5\text{Gy}} < 50 \%$ [117] [C]	
Lung	$V_{24\text{Gy}} < 30\%$ [20] [A]	
Optic pathway	$D_{MAX} < 30 \text{ Gy}$ (optimal); [15] [D] $D_{MAX} < 45 \text{ Gy}$ (mandatory);[15,40] [B]	Retinopaty, partial blindness, cataracts.
Orbital Bone	$D_{MAX(0.1 \text{ cm}^3)} < 40 \text{ Gy-RBE}$ [118] [C]	To avoid dysmorphic alterations of the orbital bones (especially in the radiotherapy of rhabdomyosarcomas)
Pituitary Gland	$D_{MAX} < 60 \text{ Gy}$ [15] [D]; $D_{MAX} < 42 \text{ Gy}$ ; $D_{MEAN} < 25 \text{ Gy}$ [40] [B]	
Parotid Gland	$D_{MEAN} \leq 26 \text{ Gy}$ $D_{MEAN} < 40 \text{ Gy}$ (mandatory) [18] [B]	
Soft Tissues and Skeletal system	Limit $V_{25\text{Gy}}-V_{30\text{Gy}}$ [20] [A]	Limit $V_{25-30 \text{ Gy}}$ to reduce muscular hypoplasia. Avoid substantial dose gradient (> 10-15 Gy) to the spine to limit asymmetric growing (kyphosis or scoliosis). [20] [A]
Spleen	$D_{MEAN} < 10 \text{ Gy}$ [119] [A] [120] [C]	
Submandibular Gland	$D_{MEAN} \leq 26 \text{ Gy}$ [18] [B]	
Rectum	$D_{5\text{cm}^3} < 52 \text{ Gy EQD2}$ [121] [C]	Data obtained in a population of pediatric patients with pelvic tumors undergoing pulsed brachytherapy ± external beam radiotherapy
Thyroid Gland	$D_{MEAN} < 30 \text{ Gy}$ ; $D_{MEAN} < 20 \text{ Gy}$ (optimal); [16] [B]	The predicted average risk of compensated (subclinical) hypothyroidism was 25% and 44% for thyroid doses of 20 and 30 Gy, respectively. From that analysis, the expected rates of uncompensated hypothyroidism were 7% and 13% for thyroid doses of 20 and 30 Gy, respectively. [16] [B]

**Legend:** ALARA: as low as reasonably achievable; EQD2: equivalent doses per 2-Gy fractions; DMax: Maximum Dose; DMean: Mean Dose; Gy: Gray; Gy-RBE: gray relative biological equivalents. Common abbreviations were used in the tables:  $V_{\odot}$  = Volume receiving a dose  $\geq \odot \text{ Gy}$ ,  $D_{\odot\odot}$  = dose received by % of the organ volume,  $D_{\odot}$  = dose received by  $\gamma \text{ cm}^3$  (the cubic centimeters) of the organ volume,  $D_{MAX}$  = maximum dose received by the organ,  $D_{MEAN}$  = mean dose received by the organ. Volumes and doses were expressed as percentage (%) or absolute values ( $\text{cm}^3$  or Gy, respectively). The anatomical descriptions are reported in Table 2. The letters in square brackets indicate the levels of evidence, classified as follows: [A] International guidelines; [B] literature review on clinical or planning studies; [C] Data from results of clinical or planning studies; [D] expert opinions or used in prospective trials. \*considered 180-200 cGy/fraction, as defined by Marks et al [3].

**Table S5.** Specific dose-volume constraints for adult patients treated for stereotactic arrhythmia radioablation (STAR).

Organ	Constraints for single dose hypofractionation
Anterior Descending Artery	$D_{MAX(0.03 \text{ cm}^3)} \leq 12 \text{ Gy}$ [24] [B] $D_{MAX} \leq 14 \text{ Gy}$ [22] [D]
Aorta	$D_{MAX(0.1 \text{ cm}^3)} \leq 15.4 \text{ Gy}$ [6] [A];
Bowel Small	$D_{MAX(0.5 \text{ cm}^3)} < 15.4 \text{ Gy}$ (mandatory); $D_{5\text{cm}^3} < 11.9 \text{ Gy}$ (optimal) [8] [A]
Bowel Large	$D_{MAX} < 18.4 \text{ Gy}$ (mandatory); $D_{20\text{cm}^3} < 14.3 \text{ Gy}$ (optimal) [8] [A]
Chestwall	$D_{MAX(0.1 \text{ cm}^3)} < 30 \text{ Gy}$ (optimal) [6] [A]; $D_{1\text{cm}^3} < 22 \text{ Gy}$ [8] [A]
Esophagus	$D_{MAX(0.1 \text{ cm}^3)} \leq 15.4 \text{ Gy}$ [6] [A]; $V_{11.9\text{Gy}} < 5 \text{ cm}^3$ ; $V_{16\text{Gy}} < 0.03 \text{ cm}^3$ [8,21] [A]
Hearth- PTV	$D_{MAX(0.1 \text{ cm}^3)} \leq 22 \text{ Gy}$ [6] [A]; $V_{16\text{Gy}} < 15 \text{ cm}^3$ ; [8,21] [A] [23] [B] $D_{50\%} \leq 5 \text{ Gy}$ [22] [D]
Implantable Cardioverter Defibrillator (ICD)	$D_{MAX} \leq 0.5 \text{ Gy}$ [22] [D] $D_{MAX} < 2 \text{ Gy}$ [80,122] [A]
Left Circumplex Coronary Artery (CxCA)	$D_{MAX(0.03 \text{ cm}^3)} \leq 12 \text{ Gy}$ [24] [B] $D_{MAX} \leq 14 \text{ Gy}$ [22] [D]
Left Main Coronary artery (LMCA)	$D_{MAX(0.03 \text{ cm}^3)} \leq 12 \text{ Gy}$ [24] [B] $D_{MAX} \leq 14 \text{ Gy}$ [22] [D]
Liver	$V_{9.1\text{Gy}} < 700 \text{ cm}^3$ ; [6,8,21] [A]
Lung	$V_{20\text{Gy}} < 15\%$ (mandatory); $D_{MEAN} < 8 \text{ Gy}$ (mandatory); $V_{20\text{Gy}} < 10\%$ (optimal); [6] [A] $V_{7\text{Gy}} < 1500 \text{ cm}^3$ ; $V_{7.4\text{Gy}} < 1000 \text{ cm}^3$ ; [8,21] [A]
Proximal Brochus	$D_{MAX(0.1 \text{ cm}^3)} \leq 20.2 \text{ Gy}$ [6] [A] $V_{10.5\text{Gy}} < 4 \text{ cm}^3$ ; [8,21] [A]
Right Coronary Artery(RCA)	$D_{MAX(0.03 \text{ cm}^3)} \leq 12 \text{ Gy}$ [24] [B]
Skin	$D_{MAX(0.01 \text{ cm}^3)} < 26 \text{ Gy}$ (mandatory); $D_{10\text{cm}^3} < 23 \text{ Gy}$ (mandatory) [6,8] [A]
SpinalCord	$D_{MAX(0.035 \text{ cm}^3)} < 14 \text{ Gy}$ (mandatory); $D_{MAX(0.035 \text{ cm}^3)} < 12.4 \text{ Gy}$ (optimal) [6] [A] $V_{7\text{Gy}} < 1.2 \text{ cm}^3$ ;

	$V_{10Gy} < 0.35 \text{ cm}^3$ ; [8,21] [A]
Stomach	$D_{MAX(0.1 \text{ cm}^3)} < 12.4 \text{ Gy}$ (mandatory); $D_{10\text{cm}^3} < 11.2 \text{ Gy}$ (optimal) [6,8] [A]
Superior Vena cava	$D_{MAX(0.1 \text{ cm}^3)} \leq 15.4 \text{ Gy}$ [6] [A]; $D_{50\%} \leq 0.6 \text{ Gy}$ [22] [D]
Trachea	$D_{MAX} \leq 20.2 \text{ Gy}$ ; $V_{10.5Gy} < 4 \text{ cm}^3$ ; [8,21] [A]

**Legend:** CxCA: Left Circumplex Coronary Artery; DMax: Maximum Dose; Gy: Gray; ICD: implantable cardioverter defibrillator; A\_LAD: Left Anterior Descending Coronary Artery; LMCA: Left Main Coronary artery; RCA: Right Coronary Artery; PTV: Planning Target Volume. The anatomical descriptions are reported in Table 2. Common abbreviations were used in the tables:  $V_{\otimes}$  = Volume receiving a dose  $\geq \otimes$  Gy,  $D_{\otimes\otimes}$  = dose received by % of the organ volume,  $D_{\otimes}$  = dose received by  $\gamma$  cm<sup>3</sup> (the cubic centimeters) of the organ volume, DMAX = maximum dose received by the organ, DMEAN = mean dose received by the organ. Volumes and doses were ex-pressed as percentage (%) or absolute values (cm<sup>3</sup> or Gy, respectively). The letters in square brackets indicate the levels of evidence, classified as follows: [A] International guidelines; [B] literature review on clinical or planning studies; [C] Data from results of clinical or planning studies; [D] expert opinions or used in prospective trials. \* Please consider anatomical description reported in **Table1 or 2**. **Note:** other cardiac substructures (Pulmonary trunk, right and left pulmonary veins, right and left ventricles, right atrium, inferior vena cava, phrenic nerve) may be delineated for dosimetric purposes.