Supplementary material for Stokkevåg CH, et al. Estimated risk of radiation-induced cancer following paediatric cranio-spinal irradiation with electron, photon and proton therapy. Acta Oncol 2014;53: 1048–57.

Supplementary Appendix A

The OEDs were calculated by initially interpolating the discrete data points given by the treatment planning software, which were subsequently integrated using a standard numerical routine. To cross check for any systematic biases, two different interpolation methods were used, linear interpolation and piece-wise cubic Hermite polynomials; for integration the trapezoidal method, Simpson's rule and Gauss-Konrod quadrature were applied. The three different dose response models over which integration was performed are listed below.

Linear dose-response:

$$OED_{Linear} = D_{Mean} = \int_V D dV \quad (1)$$

which is the equivalent of the mean of the dose-volume distribution,

A plateau response:

$$OED_{Plateau} = \int_V [D H(4.5 - D) + 4.5 H(D - 4.5)] dV \quad (2)$$

where $H(x)$ is the Heaviside step function with threshold value at 4.5 Gy between linear and plateau response for a fractionated protocol, and an

Organ-specific linear-exponential response:

$$OED_{Lin-Exp} = \int_V D e^{-\alpha D} dV \quad (3)$$

where α is an organ specific parameter taken from [11].

Uncertainty in the dose-volume data points were taken from the width of the dose bins produced by the treatment planning software. 0.1 Gy was applied as bin width in the calculations. For the $OED_{Plateau}$ we used 4.5 ± 0.5 Gy as the confidence interval, assuming the threshold value between the linear and the plateau response is within this interval [10]. Considering the $OED_{Lin-Exp}$, the 95% confidence interval of the organ specific α parameter was used [11]. Confidence intervals for the LAR coefficients were calculated based on a log-normal distribution and using organ-specific variances of $\log(\text{LAR})$ for a population of mixed ages [22]. Estimating the absolute risk of radiation induced cancer following radiotherapy is a procedure with a great amount of inherent uncertainties. The LAR coefficients are by far the most excessive contributor to the overall uncertainty; mostly attributed to sampling variability in the parameter estimates, uncertainty in the transport models used (Excess Relative Risk and Excess Absolute Risk) and the presumed uncertainty of the DDREF.

Average doses were calculated as the mean over all six patients per organ for each treatment technique. The confidence interval was estimated by calculating the lower 0.025 and upper 0.975 quantiles of the mean statistic's distribution using the method recommended in¹. This distribution was found using an exhaustive bootstrapping procedure. For the mean dose-volume distributions we first randomly sampled the data point uncertainties before applying the bootstrap procedure, which takes into account possible binning effects.

¹Hyndman RJ, Fan Y. Sample quantiles in statistical packages. Am. Stat. 1996; **50**: 361-5.

Supplementary Appendix B

Figure B1. Mean dose-volume distributions of all patients for the lungs. The shading of each distribution extends out to the 95% confidence interval of the bootstrapped mean distribution.

Figure B4. Mean dose-volume distributions of the liver for all patients.

Figure B2. Mean dose-volume distributions of all patients for the stomach.

Figure B5. Mean dose-volume distributions of all patients for the thyroid.

Figure B3. Mean dose-volume distributions of all patients for the colon.

Figure B6. Mean dose-volume distributions of all patients for the bones.

Figure B7. Mean dose-volume distributions of all patients for the bladder. For this organ, the difference in dose distributions was quite distinct between the patients, especially for the photon treatment. This is probably due to rather large variations in the organ shape, size and location and due to a generally larger photon dose reaching these volumes. With regard to the proton techniques the bladder doses were also relatively low.

Supplementary Appendix C

Figure C1. Organ equivalent doses for the stomach grouped by technique. Results for each individual patient in sequence from left to right, female: 5 years, 7 years, 8 years, male: 8 years, 8 years, 11 years.

Figure C3. Organ equivalent doses for the thyroid.

Figure C2. Organ equivalent doses for the colon.

Figure C4. Organ equivalent doses for the bladder.

Supplementary Appendix D

Figure D1. Life attributable risk of radiation induced cancer in the stomach with 95% confidence intervals. Patient sequence from left to right, female: 5 years, 7 years, 8 years, male: 8 years, 8 years, 11 years.

Figure D3. Life attributable risk of radiation induced cancer in the liver.

Figure D2. Life attributable risk of radiation induced cancer in the thyroid.

Figure D4. Life attributable risk of radiation induced cancer in the bladder.