# Supplementary Data

Table S1. Excluded cohorts in the analysis and the reason for exclusion.

| **Patient cohort** | **# patients** | **Reason of exclusion** |
| --- | --- | --- |
| Slotman 1996 | 31 | Larger fraction size for conventional RT group (4Gy/fx) |
| Jeremic 1997 | 49 | Twice a day fractionation (bid) with 1.2 Gy/fx |
| Haffty 1988 | 43 | Three fourths of the patients (n=32) were treated with split course RT |
| Noordijk 1988 | 50 | All the patients were treated with split course RT |
| Cheung 2002 | 33 | Larger fraction size for conventional RT group (4Gy/fx) |
| Chen 2008 | 65 | Early stage outcomes could not be separated from locally advanced outcomes |
| Krol 1996 | 108 | Two thirds of the patients (n=69) were treated with split course RT |
| Hayakawa 1999 | 36 | Outlier (based on the logistic fit) |
| Sibley 1998 | 141 | Outlier (based on the logistic fit) |

Table S2. The datasets used for this analysis in three different groups based on Mehta, et al.’s data (2012) and the estimated EQD22.8 (Gy) of the best-fit by the model simulation.

| **Patient cohort** | **# pts** | **Total dosea (Gy)** | **Fraction sizea (Gy)** | **# fxs** | **Fraction scheduleb** | **Tumor control** | **Model EQD22.8 (Gy)** | **Treatment duration** | **Chemotherapy** | **Dose calculation algorithm** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Conventional RT** | | | | | | | |  |  |  |
| Kaskowitz et al. (1993) | 53 | 63.2 | 2 | 30 | 5fx/wk | 0.585 | 63.2 | 1980-1990 | None | N/S |
| Sandler et al. (1990) | 77 | 60 | 2 | 30 | 5fx/wk | 0.572 | 60.0 | 1970-1987 | N/S | N/S |
| Morita et al. (1997) | 149 | 64.7 | 2 | 32 | 5fx/wk | 0.557 | 64.7 | 1980-1989 | N/S | Lung density correction |
| Cheung et al. (2000) | 102 | 52.5 | 2.63 | 20 | 5fx/wk | 0.590 | 66.9 | 1986-1995 | None | Lung density correction |
| Yu et al. (2008) | 80 | 66.6 | 1.8 | 37 | 5fx/wk | 0.342 | 57.7 | 1/99-12/01 | None | N/S |
| Narayan et al. (2004) | 18 | 87.4c | 1.9c | 46 | 5fx/wk | 0.730 | 79.9 | N/S | 1 neo-adjuvant | Lung density correction |
| Zhao et al. (2007) | 114 | 66 | 2 | 33 | 5fx/wk | 0.502 | 66.0 | 1992-2004 | Few selected patients | Heterogeneity correction |
| NKI datad | 123 | 70.9 | 2.95 | 24 | 5fx/wk | 0.886 | 99.3 | 2008-2010 | All patients (concurrent daily low dose cisplatin) | Collapsed coneg |
| WUSTL datad | 42 | 75.8 | 2.02 | 37 | 5fx/wk | 0.691 | 75.8 | 1991-2001 | 1/3 pts got prior or concurrent chemo | Retrospective Monte Carlog |
| Gauden et al.d (1995) | 347 | 50 | 2.5 | 20 | 5fx/wk | 0.410 | 59.9 | 1/85-6/92 | None | No lung correction |
| **SBRT with several fractions (3-10 fxs)** | | | | | | | |  |  |  |
| Baumann et al. (2009) | 57 | 56.3 | 18.8 | 3 | [1 3 5] | 0.93 | 167.4 | 8/03-9/05 | None | Pencil beam with heterogeneity correction |
| Baumann et al. (2006) | 80 | 55.1 | 18.4 | 3 | [1 4 8] | 0.88e | 139.4 | 1996-2003 | None | N/S |
| 18 | 49.0 | 12.3 | 4 | [1 4 8 11] |
| 23 | 36.8 | 12.3 | 3 | [1 4 8] |
| Ricardi et al. (2010) | 62 | 50.6 | 16.9 | 3 | [1 3 5] | 0.935 | 137.6 | 5/03-8/07 | None | Superposition convolution (Collapsed cone) g |
| Fakiris et al. (2009) | 70 | 70.9 | 23.6 | 3 | [1 4 8] | 0.943 | 257.8 | N/S | None | No heterogeneity correction |
| Kopek et al. (2008) | 89 | 56.3 | 18.8 | 3 | [1 3 5] | 0.944 | 167.4 | 2000-2007 | None | N/S |
| Koto et al. (2007) | 20 | 42.8 | 14.25 | 3 | [1 3 5] | 0.71e | 98.4 | 3/98-12/04 | None | Modified Batho Power law |
| 11 | 57.0 | 7.125 | 8 | [1 2 4 5 8 9 11 12] |
| Takeda et al. (2009) | 63 | 56.3 | 11.3 | 5 | [1 3 5 8 10] | 0.952 | 117.3 | 12/01-5/07 | None | Superposition w/ heterogeneity correctiong |
| Onimaru et al. (2008) | 13 | 36.0 | 9 | 4 | [1 2 4 5] | 0.57e | 76.1 | 2/00-6/05 | None | Heterogeneity correction by Clarkson (half) or superposition (half) |
| 28 | 43.2 | 10.8 | 4 | [1 2 4 5] |
| Nagata et al. (2005) | 45 | 43.2 | 10.8 | 4 | [1 5 8 12] | 0.98 | 94.9 | 9/98-2/04 | None | N/S (CADPlan V.3.1) |
| Salazar et al. (2008) | 60 | 48.6 | 12.14 | 4 | [1 8 15 22] | 0.98 | 127.8 | 5/00-3/07 | N/S | N/S |
| Chang et al. (2008) | 7 | 44.2 | 11.1 | 4 | [1 2 3 4] | 0.875e | 117.8 | 2004-2007 | Some of the 14 recurrent pts might get previously | Heterogeneity correction |
| 20 | 55.3 | 13.8 | 4 | [1 2 3 4] |
| Hoyer et al. (2006) | 40 | 37.5 | 12.5 | 3 | [1 4 8] | 0.925 | 83.0 | 1/00-9/03 | None | N/S (Helax, TMS or CADPlan Plus/Eclipse) |
| Lagerwaar et al. (2008) | 93 | 67.5 | 22.5 | 3 | [1 4 8] | 0.97e | 187.6 | N/S | 3/219 pts got in the prior treatment | N/S (BrainScan V.5.2) |
| 99 | 67.5 | 13.5 | 5 | [1 3 5 8 10] |
| 27 | 67.5 | 8.4 | 8 | [1 2 4 5 8 9 11 12] |
| Ng et al. (2008) | 2 | 51.4 | 12.9 | 4 | [1 4 8 11] | 0.90e | 185.0 | 2000-2003 | None | Heterogeneity correction (BrainScan V.3.51) |
| 4 | 48.2 | 16.1 | 3 | [1 8 15] |
| 2 | 64.3 | 16.1 | 4 | [1 4 8 11] |
| 12 | 57.9 | 19.3 | 3 | [1 8 15] |
| Xia et al. (2006) | 43 | 75.0 | 7.5 | 10 | [1 2 3 4 5 8 9 10 11 12] | 0.95 | 127.3 | 6/00-5/03 | None | N/S (Gammaknife) |
| Yoon et al. (2006) | 3 | 31.7 | 10.6 | 3 | [1 2 3] | 0.81e | 87.7 | 1/98-2/04 | None | N/S (Render Plan) |
| 10 | 42.2 | 10.6 | 4 | [1 2 3 4] |
| 8 | 50.7 | 12.7 | 4 | [1 2 3 4] |
| Zimmerman et al. (2006) | 43 | 50.0 | 16.7 | 3 | [1 4 8] | 0.941 | 118.2 | 12/00-1/06 | None | Pencil beam (Helax) |
| 25 | 46.7 | 9.3 | 5 | [1 3 5 8 10] |
| van der Voort van Zyp et al. (2009) | 10 | 51.5 | 17.2 | 3 | [1 3 5] | 0.943e | 228.8 | 8/05-10/07 | None | Equivalent path length for heterogeneity correction |
| 59 | 68.7 | 22.9 | 3 | [1 3 5] |
| Song et al. (2009) | 12 | 43.5 | 10.9 | 4 | [1 2 3 4] | 0.875e | 116.9 | 6/99-5/06 | None | N/S (Render 3D or Eclipse) |
| 16 | 52.2 | 13.1 | 4 | [1 2 3 4] |
| 4 | 65.3 | 21.8 | 3 | [1 2 3] |
| Timmerman et al. (2010) | 55 | 55.4 | 18.5 | 3 | [1 5 10] | 0.945 | 167.2 | 5/04-10/06 | None | Heterogeneity correction based on RTOG 0236 |
| Haasbeek et al. (2010) | 69 | 67.5 | 22.5 | 3 | [1 3 5] | 0.969e | 182.0 | 2003-2008 | None | N/S (BrainScan V.5.31) |
| 101 | 67.5 | 13.5 | 5 | [1 3 5 8 10] |
| 33 | 67.5 | 8.4 | 8 | [1 3 5 8 10 12 15 17] |
| Guckenberger et al. (2009) | 6 | 46.4 | 7.7 | 6 | [1 3 5 8 10 12] | 0.927e | 108.1 | 1997-2007 | None | Heterogeneity correction based on collapsed coneg |
| 6 | 38.1 | 12.7 | 3 | [1 3 5] |
| 23 | 46.6 | 15.5 | 3 | [1 3 5] |
| 6 | 29.3 | 29.3 | 1 | [1] |
| **Single-fraction SBRT** | | | | | | | |  |  |  |
| Hof et al. #1f (2007) | 10 | 20.7 | 20.7 | 1 | [1] | 0.600 | 63.2 | 10/98-11/05 | None | Pencil beam |
| Hof et al. #2f (2007) | 32 | 25.2 | 25.2 | 1 | [1] | 0.938 | 90.0 |
| Le et al. #1f (2006) | 7 | 17.9 | 17.9 | 1 | [1] | 0.430 | 47.2 | 5/00-4/05 | 9 recurrent pts got previously | Pencil beam (effective path-length) |
| Le et al. #2f (2006) | 13 | 29.9 | 29.9 | 1 | [1] | 0.923 | 127.4 |
| Fritz et al. (2008) | 40 | 27 | 27 | 1 | [1] | 0.925 | 105.2 | N/S | None | Pencil beam w/ Batho law correction |
| Pennathur et al. (2009) | 17 | 22.5 | 22.5 | 1 | [1] | 0.471 | 73.7 | 2002-2005 | None | N/S (Cyberknife) |
| a Normalized as the average of the dose at the isocenter and the dose at the PTV margin based on the prescription information.  b For SBRT regimes, the schedules were given as the date of fractionation. For example, [1 3 5] means that the RT fractions were given on day 1, 3, and 5 (c.f. Mon, Wed, and Fri).  c Adjusted based on the reported lung density correction in the report (2.1 Gy/fx in lung is equivalent to about 1.9 Gy/fx).  d Added datasets.  e Only total outcome was reported for several different fractionation schemes and the individual model equivalent doses were averaged with population-based weighting to estimate the overall model equivalent dose of the total patient cohort.  f In these studies, the separate outcomes were available for different regimes.  g convolution or superposition dose calculation algorithms, which are known to be more accurate  N/S: not specified. | | | | | | | | | | |

Table S3. The additional datasets used for external validation of the model analysis.

| **Patient cohort** | **# pts** | **Total dosea (Gy)** | **Fraction sizea (Gy)** | **# fxs** | **Fraction scheduleb** | **Tumor control** | **Model EQD22.8 (Gy)** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Stephans et al. #1c (2009) | 56 | 50.8 | 10.15 | 5 | [1 2 3 4 5] | 0.964 | 95.2 |
| Stephans et al. #2 c (2009) | 38 | 70.2 | 23.39 | 3 | [1 5 10] | 1.000 | 255.8 |
| Olsen et al. (2011) | 111 | 64.3 | 21.43 | 3 | [1 4 8] | 0.939d | 204.1 |
| 8 | 53.6 | 10.71 | 5 | [1 4 8 11 15] |
| 11 | 59.5 | 11.9 | 5 | [1 4 8 11 15] |
| Shibamoto et al. (2012) | 4 | 39.6 | 9.9 | 4 | [1 4 8 11] | 0.856d | 92.9 |
| 124 | 43.2 | 10.8 | 4 | [1 4 8 11] |
| 52 | 46.8 | 11.7 | 4 | [1 4 8 11] |
| Chang et al. (2012) | 130 | 60.6 | 15.15 | 4 | [1 2 3 4] | 0.985 | 153.3 |
| Mutter et al. (2012) | 73 | 60.0 | 20 | 3 | [1 3 5] | 0.952d | 140.1 |
| 54.0 | 18 | 3 | [1 3 5] |
| 38 | 48.0 | 12 | 4 | [1 3 5 8] |
| 15 | 45.0 | 9 | 5 | [1 3 5 8 10] |
| Shirata et al. (2012) | 45 | 45.6 | 11.4 | 4 | [1 2 3 4] | 0.926d | 88.8 |
| 29 | 57.0 | 7.13 | 8 | [1 2 3 4 5 8 9 10] |
| 7 | 57.0 | 3.8 | 15 | 5fx/wk |
| Taremi et al. #1c (2012) | 43 | 48.0 | 12 | 4 | [1 3 5 8] | 0.954 | 103.4 |
| Taremi et al. #2c (2012) | 20 | 54.0 | 18 | 3 | [1 3 5] | 0.950 | 155.6 |
| Taremi et al. #3c (2012) | 31 | 60.0 | 20 | 3 | [1 3 5] | 1.000 | 187.8 |
| Taremi et al. #4c (2012) | 9 | 60.0 | 7.5 | 8 | [1 2 3 4 5 8 9 10] | 0.778 | 95.9 |
| Taremi et al. #5c (2012) | 11 | 50.0 | 5 | 10 | [1 2 3 4 5 8 9 10 11 12] | 0.546 | 68.0 |
| Fischer-Valuck et al. #1c (2013) | 13 | 48.0 | 12 | 4 | [1 4 8 11] | 0.846 | 107.0 |
| Fischer-Valuck et al. #2c (2013) | 49 | 60.0 | 12 | 5 | [1 4 8 11 15] | 0.959 | 147.2 |
| Inoue et al. (2013) | 30 | 48.0 | 12 | 4 | [1 2 4 5] | 0.810d | 98.4 |
| 79 | 47.5 | 11.88 | 4 | [1 2 4 5] |
| Jeppesen et al. #1c (2013) | 32 | 37.8 | 12.6 | 3 | [1 5 9] | 0.830d | 139.0 |
| 1 | 42.1 | 14.03 | 3 | [1 5 9] |
| 67 | 55.4 | 18.48 | 3 | [1 5 9] |
| Jeppesen et al. #2c (2013) | 20 | 80.2 | 2.29 | 35 | 5fx/wk | 0.781d | 89.4 |
| 12 | 80.0 | 2 | 40 | 5fx/wk |
| Hayashi et al. (2014) | 60 | 48.0 | 12 | 4 | [1 4 8 11] | 0.926d | 106.0 |
| 21 | 60.0 | 6 | 10 | [1 2 4 5 8 9 11 12 15 16] |
| Videtic et al. (2014) | 55 | 33.8 | 33.8 | 1 | [1] | 0.888d | 175.8 |
| 25 | 37.9 | 37.9 | 1 | [1] |
| Kelley et al. (2015) | 66 | 53.3 | 13.33 | 4 | [1 2 3 4] | 0.909 | 119.8 |
| Nagata et al. (2015) | 169 | 48.0 | 12 | 4 | [1 2 4 5] | 0.882 | 99.7 |
| Videtic et al. #1c (2015) | 33 | 45.3 | 45.33 | 1 | [1] | 0.970 | 287.0 |
| Videtic et al. #2c (2015) | 41 | 64.0 | 16 | 4 | [1 2 3 4] | 0.927 | 167.6 |
| a Normalized as the average of the dose at the isocenter and the dose at the PTV margin based on the prescription information, when the relevant information is available.  b The schedules were given as the date of fractionation. For example, [1 3 5] means that the RT fractions were given on day 1,3, and 5.  c In these studies, the separate outcomes were available for different regimes.  d For the total outcome for several different fractionation schemes, the individual model equivalent doses were averaged with population-based weighting to estimate the overall model equivalent dose of the total patient cohort. | | | | | | | |



Figure S1. Deviations of estimated EQD210,model from BED. These figures show the ratio of EQD210,model/BED, depending on (A) number of fractions, (B) treatment duration, and (C) the fractional dose. Lower efficacies (with lower ratios of EQD210,model/BED) were observed with a smaller number of fractions, shorter treatment duration, and larger fraction size, when evaluated with the hypoxia, proliferation, and cell cycle effects in the model. The efficacy of single SBRT was minimum with the average ratio of 0.49 (open circle). BED does not account for radiosensitivity, heterogeneity, or proliferation.



Figure S2. Dose-response curves estimated from maximum likelihood method based on the EQD210,model values, with an *γ50* value of 1.5 for total group: (A) for reference radiosensitivity values of α value of 0.35, α/β ratio of 10, and OERI of 2; and (B) for the best-fit parameter values of α value of 0.305, α/β ratio of 2.8, and OERI of 1.7.



Figure S3. Estimation of the 95% confidence intervals of TD50 values based on the profile likelihood method: (A) conventional RT group; (B) multi-fx SBRT group; (C) single-fx SBRT group; and (D) total group.



Figure S4. Dose-response curves obtained by applying other models to the dataset of current study: (A) Shuryak *et al.*’s model (69); and (B) Tai *et al.*’s model (70).