

Estimating the Tolerance of Brachial Plexus to Hypofractionated Stereotactic Body Radiotherapy – A Modelling-based Approach from Clinical Experience.

Irina Kapitanova

Mount Sinai Saint Luke's

Sharmi Biswas

Weill Cornell Medicine

Sabrina Divekar

Tel Aviv University School of Medicine

Eric J Kemmerer

Geisinger Health System

Robert A Rostock

Geisinger Health System

Kenneth M Forster

Geisinger Health System

Rachel J Grimm

Thomas Jefferson Hospital

Carla J Scofield

Geisinger Health System

Jimm Grimm (✉ JimmGrimmJr@yahoo.com)

Geisinger Health System <https://orcid.org/0000-0003-1962-3139>

Bahman Emami

Loyola University

Anand Mahadevan

Geisinger Health System

Research

Keywords: Body Radiotherapy, Brachial Plexus, hypofractionated Stereotactic, Oncology

Posted Date: November 2nd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-100186/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Radiation Oncology on June 7th, 2021. See the published version at <https://doi.org/10.1186/s13014-021-01822-5>.

Abstract

Background: Brachial plexopathy (BP) is a potentially serious complication from stereotactic body radiation therapy (SBRT) that has not been widely studied. Therefore, we compared datasets from two different institutions and generated a brachial plexus dose-response model, to quantify what dose constraints would be needed to minimize the effect on normal tissue while still enabling potent therapy for the tumor.

Methods: Two published SBRT datasets were pooled and modeled from patients treated with SBRT at Indiana University and the Richard Roudebush VAMC from 1998 to 2007, as well as the Karolinska Institute from 2008 to 2013. All patients in both studies were treated with SBRT for apically located lung tumors localized superior to the aortic arch. Toxicities were graded according to Common Terminology Criteria for Adverse Events (CTCAE) and a probit dose response model was created with maximum likelihood parameter fitting.

Results: This analysis includes a total of 89 brachial plexus Dmax values from both institutions. Among the 14 patients who developed BP, the most common complications were grade 2, comprising 7 patients. The median follow-up was 30 months (range 6.1-72.2) in the Karolinska dataset, and Indiana had a median of 13 months (range 1-71). Both studies had a median range of 3 fractions, but in the Indiana dataset 9 patients were treated in 4 fractions and the paper did not differentiate which ones were which, so our analysis is considered to be in 3-4 fractions, which is one of the main limitations. The probit model showed that the risk of BP with Dmax of 26 Gy in 3-4 fractions is 10%, and 50% with Dmax of 70 Gy in 3-4 fractions.

Conclusions: This analysis is only a preliminary result because more details are needed, and more comprehensive datasets are needed from a much broader cross-section of clinical practices. When more institutions join the QUANTEC and HyTEC methodology of reporting sufficient details to enable data pooling, our field will finally reach an improved understanding of human dose tolerance.

Background

Stereotactic body radiation therapy (SBRT) is a treatment option increasingly used for patients with lung cancer, including apical lung tumors, who are not surgical candidates. The main objective of the treatment is to provide the most effective SBRT dose on the tumor with minimal effect on normal tissue while avoiding post-radiation complications. Based on the tumor location (proximal of the brachial plexus), tumor size, dose, and numerous other factors, a potentially severe adverse effect after SBRT is radiation induced brachial plexopathy (RIBP) (1, 2). Onset of RIBP symptoms may occur from months to years after the radiotherapy (3). Brachial Plexopathy, as defined in the Common Terminology Criteria for Adverse Events (CTCAE) v.5 (4), may include muscle weaknesses of the upper limbs, neuropathic pain, limitation of movement, paresthesia and wasting. Understanding the tradeoffs between benefit and risk

in SBRT dose and fractionation can provide clarity by considering the range of severity of the symptoms, from asymptomatic to full loss of movement of the upper extremity.

In 1991 the Emami paper (5) recommended a 5% risk in 5-year tolerance dose (TD 5/5) on the entire brachial plexus to be 60 Gy in conventional fractionation, based on expert opinion and on dose-response models (6). Just 3 years later, the first clinical stereotactic body radiation therapy (SBRT) paper (7) included a dose-response model (8) to guide the clinical practice, and a recent dose-response model for brachial plexus has been published (2) by the same institution. After a quarter of a century of SBRT practice, other studies validating this are lacking and will be needed to definitively determine tolerance of brachial plexus to SBRT. North American clinical trials for stereotactic ablative body radiotherapy (SABR) began at Indiana University (9) and the brachial plexus dose and toxicity outcome for each patient in a cohort was published (1). From that work, the two datasets have been pooled and analyzed as recommended by QUANTEC methodology (10–11). If this was standard practice in radiation oncology, then our understanding of human dose tolerance of various normal tissues to radiation would be vastly improved. Unfortunately these examples are the extreme rarity, to the degree that, although a PubMed search of (SBRT OR SABR) AND (spinal cord) returns more than 250 papers, the High Dose per Fraction, Hypofractionated Treatment Effects in the Clinic (HyTEC) effort was only able to find 3 papers (12) that provided full datasets with critical structure dose and toxicity outcome per patient for spinal cord, which only represents about 1% of the published literature.

If detailed reporting of spinal cord is so rare, even though it is among the most important critical structures in the body, it will be even harder to accumulate sufficient data for other organs. Therefore, is it possible to create comprehensive Emami-style dose tolerance limits (5) for intricate structures such as brachial plexus? The goal of the dose volume histogram (DVH) Risk Map (13) is to provide a modernized graphical view of Emami-style unified low- and high-risk limits, along with a numerical summary of the constraints and estimates of associated risk. This paper summarizes initial steps towards creation of the DVH Risk Map for brachial plexus, as an impetus to improve data reporting across published literature for better understanding of tolerance levels.

Methods

To identify brachial plexus dose tolerance after SBRT based on dose-response models of clinical outcomes data, the following 6 elements are needed: 1) dose to the brachial plexus, 2) fractionation, 3) volume, 4) endpoint, 5) follow-up time, and 6) incidence of the endpoint occurring within the follow-up time (13). These 6 items are needed per patient, or at least stratified into small groups of patients with similar characteristics. A PubMed search for (brachial plexus) AND (stereotactic OR SABR OR SBRT) was performed and 52 papers were found as of July 2020, but only two of the studies came close to providing the needed information for all patients in a study.

The two datasets were comprised of patients treated with SBRT 1) at Indiana University and the Richard Roudebush VAMC from 1998 to 2007 (1) as well as 2) the Karolinska Institute from 2008 to 2013 (2). All

patients in both studies were treated with SBRT for apically located lung tumors localized superior to the aortic arch. A total of 89 patients (with 93 lesions) from both institutes received SBRT and were included in this analysis.

Physical dose without any biological conversions was used in the graph of presented brachial plexus maximum doses in the Indiana dataset, and the linear quadratic (LQ) model (14–15) as well as the universal survival curve (USC) (16) were used to assess the data. In the Karolinska dataset, dose-response models were created using both the LQ and USC models. The probit dose-response model (17) was used in the Lindberg et al (2) study, so was also used in our pooled model for consistency. Maximum likelihood parameter fitting (18) was used to determine the values for the probit model (17), and confidence intervals were constructed using the profile likelihood method (19, 20).

All clinical data were collected from the patient records and graded using the Common Terminology Criteria for Adverse Events (CTCAE). Only toxicities of Grade 2 and greater in both studies were scored as complications. Indiana University used CTCAE version 3.0 (21) with scoring of grade 1–4 while Karolinska used CTCAE version 4.0 (22). CTCAE version 3.0 focused more on the symptoms affecting activities of daily living while version 4 stressed the severity of the symptoms. For the purpose of inclusion, we have also included the Modified Late Effects Normal Tissue - Subjective Objective Management Analytic (LENT-SOMA) scale (23, 24) to compare the brachial plexus adverse effects. The details of the grading of toxicity are shown in Table 1. The following variables were considered in the comparison of toxicity rates: gender, age, histology, number and size of tumors, dose of SBRT, number of fractions, and time to BP toxicity from SBRT. The Fisher Exact Test was used to assess significance among individuals with toxicity and those without toxicity (25).

Table 1
Endpoint definitions: Brachial plexus toxicity grading scales

	CTCAE Version 3.0 (21)	CTCAE Version 4.0 (22)	Modified LENT-SOMA scale (23)
Grade 1	Asymptomatic brachial plexopathy	Asymptomatic effects	Mild sensory deficits, no pain, no treatment required
Grade 2	Symptomatic brachial plexopathy without interfering with activities of daily living (ADL)	Moderate symptoms limiting ADL	Moderate sensory deficits, tolerable pain, mild arm weakness
Grade 3	Symptomatic brachial plexopathy and interfering with ADL	Severe symptoms limiting self care ADL	Continuous paresthesia, with incomplete paresis, pain medication required
Grade 4	Disabling brachial plexopathy	N/A	Complete paresis, excruciating pain, muscle atrophy, regular pain medication required
<i>Abbreviations:</i> CTCAE = Common Terminology Criteria for Adverse Events; LENT = Late Effects Normal Tissues; SOMA = Subjective, Objective, Management, Analytic; ADL = activities of daily living.			

Results

Patient characteristics, SBRT doses, and grading of radiation induced brachial plexopathy are compared in Table 2 for both studies. There was a total of 89 patients included in the study with the median age of 72 and 73 for Karolinska University and Indiana University, respectively. 93 tumors were treated in total with 22 patients having metastases.

Table 2
Apical Lesion Patient Characteristics

		Indiana University	Karolinska University	Total
Number of Patients		37	52	89
Gender	Male	21	23	44
	Female	16	29	45
Age at treatment, median (range)		73 (57–81)	72 (35–88)	
Number of tumors		37	56	93
Primary lung cancer (Squamous, NSCLC, Adenocarcinoma)		37	30*	67
Metastases		0	22	22
Tumors	Right	21	28	49
	Left	16	28	44
Volume cc, median (range)		GTV 13 (1-113)	CTV 9.1 (0.10–74.5)	
Follow-up months, median (range)		13 (1–71)	30 (6.1–72.2)	
Total treatment dose (Gy), median (range)		57 (30–72)	Median 45 Gy in 3 fx BED10 Range: 95–138 Gy	
Median dose per fraction (Gy), (range)		19 (10–24)	15 (6–17)	
Median number of fraction (range)		3 (3–4)	3 (3–10)	
Number of Patients with Brachial Plexopathy	Total	7	7	14
	Grade 2	4	3	7
	Grade 3	2	4	6
	Grade 4	1	0	1
BP development in months post-SBRT, median (range)		7 (6–23)	5.8 (0.7–13)	
*One patient with metastasis later on				
<i>Abbreviations:</i> NSCLC = non-small cell lung cancer; GTV = gross tumor volume; CTV = clinical tumor volume; fx = fractions; BED10 = biological effective dose with $\alpha/\beta=10$ Gy.				

Dose, fractionation, and volume of the brachial plexus

At Indiana University, the median prescribed treatment dose was 57 Gy in 3–4 fractions and the maximum brachial plexus dose ranged from 6 to 83 Gy (median, 26 Gy) in 3–4 fractions. The Indiana University dataset had 37 brachial plexus maximum point dose (D_{max}) values (for 36 patients) that were all included in the model. The paper did not report which patients received 3 or 4 fractions, or volume information, and these are the main limitations of the study (1). Both published datasets (1, 2) used biological conversions with $\alpha/\beta = 3$ Gy. According to the linear quadratic model (14–15), the 2 Gy per day equivalent EQD2 = 60 Gy Emami brachial plexus limit (5) corresponds to a biological effective dose (BED) of 100 Gy. In 3 fractions, LQ equates this to 26 Gy, so this was initially used as a cutoff point of risk analysis (1).

The Karolinska group used 45 Gy in 3 fractions for 80% of the cases, therefore that also was the median prescription. One patient was treated with 60 Gy in 10 fractions, six were treated with 56 Gy in 8 fractions, and the rest were in 3–5 fractions. The authors performed analysis with both USC and LQ models and found no major difference between the two for their data, so presented the data in terms of BED3 with the LQ model. Brachial plexus maximum point dose (D_{max}) ranged from BED3 = 0.10–524 Gy, which we converted to 3-fraction equivalent dose since the median number of fractions in both studies was 3. The Karolinska dataset presented model parameters for D_{max} as dose to hottest X cc (D_x) for D0.1 cc, D1cc and D3cc, but the Indiana dataset only had D_{max} . Therefore, the pooled model has no volume information, and consists of maximum point doses only.

Endpoint, Follow-up time, and estimated risk of the endpoint occurring within the follow-up time

Median range of follow up was longer in Karolinska with 30 months (range 6.1–72.2) while Indiana had a median of 13 months (range 1–71). Among the 89 patients included in both studies, 14 of them developed CTCAE grade 2 or higher RIBP, acknowledging the differences among the endpoint definitions in Table 1. Among the 14, the most common complications were grade 2, comprising 7 patients. Only 1 patient from Indiana University was recorded with grade 4 disabling RIBP described as shoulder ache progressing to paresthesia and further worsening to arm and hand wasting. This case corresponded to brachial plexus D_{max} of 76 Gy. One patient from Karolinska also noted signs of RIBP 13 months post SBRT further progressing to total paralysis of the arm, but was scored as grade 3 since CTCAE 4.0 is without grade 4 RIBP; LENT-SOMA is a useful point of comparison in this regard as shown in Table 1.

It is also important to note that in the Karolinska study, 13 patients underwent additional radiotherapy to the lung ipsilateral to the tumor site that is not included in the model in Fig. 1. Out of the 13, 10 of the patients had very low additional brachial plexus dose, $D_{max} \text{ BED}_3 \leq 3.1$ Gy. The remaining 3 had a prior conventional dose of $D_{max} \text{ BED}_3 = 90–123$ Gy with only 1 patient from this subset developing RIBP. Therefore, for the Karolinska study, 6 out of 7 patients developed RIBP strictly only from the SBRT.

Dose-response model and DVH Risk Map

Given the approximation of the 6 elements needed for a dose-response model (13), and considering their limitations, caveats, and confounding factors as enumerated above and described in the discussion, a pooled dose-response model was created. According to the fitted probit model (17, 18–20), the dose corresponding to 50% risk of complications was 70.2 Gy (95% CI: 55–116 Gy), and the slope parameter at this dose was 0.4896 (95% CI: 0.35–0.74). The model (17, 18) and 95% confidence intervals (19, 20) are depicted in Fig. 1, p -value = 0.0035, Fisher Exact Test (25). The 5% and 10% risk levels were 13.7 Gy and 26 Gy, respectively, in 3–4 fractions.

The connection between dose/volume, fractionation, and incidence of complications for the endpoint of grade 2 or higher brachial plexopathy is summarized in the form of a DVH Risk Map (13) in Fig. 2. This map includes a graph of published dose constraints in the upper portion of the figure, as well as a numerical summary of low- and high-risk constraints in the lower portion of the figure, with the resultant estimates of risk from the pooled model from Fig. 1. Appendix Fig. A1 shows how the 5% and 50% risk levels at 5 years (TD 5/5 and TD 50/5) in the Emami paper (5) were obtained from expert opinion and models in the Burman paper (6). Similarly, risk levels in the DVH Risk Map in Fig. 2 are interpolated from the dose-response model of Fig. 1.

The DVH Risk Map in Fig. 2 shows the number of fractions on the x-axis and the raw total physical dose without any BED conversion on the y-axis. Each of the five panels specifies a dose/volume metric including dose for the 50% and 10% volumes, as well as D3cc, D1cc, and Dmax. Published dose constraints from Appendix Table A1 are plotted as blue diamond marks on the map (Fig. 2). These constraints were partitioned into low- and high-risk categories from among the more established limits, represented as the circled selected limits with labels. The red X represents the dose at which a published Adverse Event (AE) occurred, as may be seen in Appendix Table A1. For visualization, a trendline of low- and high-risk are drawn as the dashed green and solid red lines in this map. Although the partitioning is somewhat arbitrary, this is approximately analogous to the TD5/5 and TD 50/5 Emami limits for conventional fractionation, but now customized to the published limits in a more useful clinical range of practice. Based on the pooled dataset, as may be seen from the tabular portion of Fig. 2, the low-risk trend of brachial plexus Dmax in 3–4 fractions is about 10% risk and the high-risk trend is about 15% risk.

Discussion

Bias and uncertainty can result from single institution non-randomized heterogeneous mixtures of patients with varying follow-up times and unknown censoring of competing risks. Throughout the past quarter of a century, over a million patients have been treated with radiosurgery on Gamma Knife alone (26), over a million more patients have been treated with SBRT on CyberKnife alone (27), and countless more have been treated on stereotactically capable linear accelerators. No excuse remains for there to be only two limited published datasets for an important critical structure like brachial plexus. It is imperative that the field of radiation oncology collects data more rigorously as highlighted by the lessons of QUANTEC (11, 10) and as continues to be emphasized by all the HyTEC papers (12, 28). In the meantime it is important to glean as much information as possible from the sparse datasets that do exist, and to

pool them into increasingly larger datasets (10). A full de-identified database of 197 patients with dosimetric information and outcome for each patient was published more than 100 years ago (29), showing that it is possible to accomplish this without sophisticated algorithms. One of the first dose-response models was created more than 90 years ago from clinical data by hand on graph paper (30) even before the first electronic computer was invented; with modern automated algorithms there is no excuse to not save and analyze the data in properly designed studies with actuarial outcomes at specific time points in multiple institutions with large cohorts of data.

The dose-tolerance numbers for conventional fractionation from the Emami paper were based on expert opinion over 30 years ago, in terms of the radiation dose limits for 1/3, 2/3/ and 3/3 organ volume, with the probability of 5% (TD 5/5) or 50% (TD 50/5) risks of complications within a 5-year follow-up. The original paper did emphasize the need for more research and available data. Two decades later the ensuing accumulated published data was consolidated into QUANTEC (32) which was much more accurate owing to the growing body of cooperative trials and institutional studies. However, the improved accuracy of QUANTEC also came with increased complexity and varied format of the limits, which is difficult to use in a day to day clinical work. The goal of the DVH Risk Map (13) is to balance the convenience of a unified framework of dose tolerance limits in low-risk and high-risk categories, with the accuracy of dose-response modeling from all the emerging published clinical data, particularly in the setting of hypofractionated SBRT.

Brachial plexus dose tolerance for conventional fractionation has been studied (5, 33–34) and contouring guidelines are available (2, 35–36). The Emami limit for brachial plexus of EQD2 = 60Gy (5) corresponds to 26 Gy in 3 fractions, which is remarkably the same dose limit as recommended in the Indiana study (1). However, the paradigm has transformed from allowing 100% organ exposure at that dose in conventional fractionation (5), now all the way down to the 0% volume at the same dose for SBRT (1, 37).

About one third of the combined dataset had Dmax values in excess of 10 Gy per fraction, where the LQ model has been questioned (16). For this reason the Karolinska authors compared LQ to USC, and found no major difference for this data (2). The Indiana dataset being in terms of physical dose avoids the BED question, but is itself a major limitation of the pooled model.

Limitations of both studies include basing the data on a small cohort of patients with limited follow up. These data may not reflect the full incidence of toxicity after SBRT, because many patients might not survive long enough for the toxicity to develop or may be lost to follow-up for a variety of reasons. Another limitation is the usage of re-irradiation for some of the Karolinska cases, although this only caused one of the complications, so insufficient data were available to construct a model that could account for re-irradiation tolerance. Differences in grading of complications was acknowledged, which may contribute to inaccurate causal analysis. Half of the complications were grade 2 and only one potentially grade 4 paresis was reported in each of the two studies, but the studies did not indicate the specific grade for each Dmax value of the whole dataset so there is no way to create separate models for each grade, as was done in a brain dose tolerance study (38) for example. Furthermore, as noted in

Table 1, the grading scales vary especially for the higher-grade events. A risk of 10% is higher than ideal for brachial plexus, but until the grade of each patient is reported in a consistent scale, clinicians must use their own judgement when interpreting the results.

Conclusions

For lung cancers near the apical region, brachial plexopathy is a major concern for high-dose radiation therapy. Based on our analysis of published data, the risk of grade 2 or higher brachial plexus toxicity after SBRT is approximately 5%, 10%, and 50% at 13.7, 26, and 70 Gy, respectively, in 3–4 fractions, but risk of grade 3 or 4 toxicity remains unknown. This paper is not intended to be a final answer, but rather an appreciation of recent efforts and a plea for more data: it is commendable that the Indiana and Karolinska authors published the data that enabled this pooled model, as recommended by QUANTEC and HyTEC. When more institutions join the QUANTEC and HyTEC methodology of reporting sufficient details to enable data pooling, our field will finally reach an improved understanding of human dose tolerance.

Declarations

Ethics approval and consent to participate

Not applicable, since data was existent in the literature

Consent for publication

Not applicable, since the manuscript does not contain data from any individual person

Availability of data and material

The datasets generated during and/or analysed during the current study are available in the published literature

Competing interests

IK, SB, SD, EJK, RAR, KMF, RJG, CJS, BE, AM: None

JG: Grants from Accuray, grants from NovoCure, outside the submitted work; In addition, Dr. Grimm has a patent DVH Evaluator issued.

Funding

None

Authors' contributions

All authors contributed to the study concept, drafting and editing the manuscript, and approved the final version for publication. IK, SB, PL, SD, and JG performed the literature review. RJG analyzed the data and created the dose-response model. IK, SB, PL and SD created the first 10 revisions of the paper. EJK, RAR, KMF, RJG, CJS, JG, BE, AM provided initial clinical input after the 10th revision. AM, and BE are the senior authors of the work and made major edits especially toward completion of the work.

Acknowledgements

The authors would like to thank Dr. Paula Lim, MD for working on the manuscript.

References

1. Forquer JA, Fakiris AJ, Timmerman RD, Lo SS, Perkins SM, McGarry RC, Johnstone PA. Brachial plexopathy from stereotactic body radiotherapy in early-stage NSCLC: dose-limiting toxicity in apical tumor sites. *Radiother Oncol*. 2009 Dec;93(3):408-13.
2. Lindberg K, Grozman V, Lindberg S, Onjukka E, Lax I, Lewensohn R, Wersäll P. Radiation-induced brachial plexus toxicity after SBRT of apically located lung lesions. *Acta Oncol*. 2019 Aug;58(8):1178-1186.
3. Fathers E, Thrush D, Huson SM, Norman A. Radiation-induced brachial plexopathy in women treated for carcinoma of the breast. *Clin Rehabil*. 2002;16(2):160-165. doi:10.1191/0269215502cr470oa
4. National Cancer Institute. Common Terminology Criteria for Adverse Events v5.0. November 27, 2017 (Accessed at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)
5. Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, Shank B, Solin LJ, Wesson M. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys*. 1991 May 15;21(1):109-22.
6. Burman C, Kutcher GJ, Emami B, Goitein M. Fitting of normal tissue tolerance data to an analytic function. *Int J Radiat Oncol Biol Phys*. 1991 May 15;21(1):123-35.
7. Lax I, Blomgren H, Näslund I, Svanström R. Stereotactic radiotherapy of malignancies in the abdomen. Methodological aspects. *Acta Oncol*. 1994;33(6):677-83.
8. Lawrence TS, Ten Haken RK, Kessler ML, Robertson JM, Lyman JT, Lavigne ML, Brown MB, DuRoss DJ, Andrews JC, Ensminger WD, et al. The use of 3-D dose volume analysis to predict radiation hepatitis. *Int J Radiat Oncol Biol Phys*. 1992;23(4):781-8.
9. Timmerman R, Papiez L, McGarry R, Likes L, DesRosiers C, Frost S, Williams M. Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. *Chest*. 2003 Nov;124(5):1946-55.
10. Deasy JO, Bentzen SM, Jackson A, Ten Haken RK, Yorke ED, Constone LS, Sharma A, Marks LB. Improving normal tissue complication probability models: the need to adopt a "data-pooling" culture. *Int J Radiat Oncol Biol Phys*. 2010 Mar 1;76(3 Suppl):S151-4.

11. Jackson A, Marks LB, Bentzen SM, Eisbruch A, Yorke ED, Ten Haken RK, Constine LS, Deasy JO. The lessons of QUANTEC: recommendations for reporting and gathering data on dose-volume dependencies of treatment outcome. *Int J Radiat Oncol Biol Phys*. 2010 Mar 1;76(3 Suppl):S155-60.
12. Sahgal A, Chang JH, Ma L, Marks LB, Milano MT, Medin P, Niemierko A, Soltys SG, Tomé WA, Wong CS, Yorke E, Grimm J, Jackson J. Spinal cord dose tolerance to stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys*. 2019 Oct 14. [HyTEC issue, In Press].
13. Asbell SO, Grimm J, Xue J, Chew MS, LaCouture TL. Introduction and Clinical Overview of the DVH Risk Map. *Semin Radiat Oncol*. 2016 Apr;26(2):89-96.
14. Fowler JF, Stern BE. Dose-rate factors in integral dose estimations [letter]. *Br J Radiol* 1958;31:316.
15. Fowler JF. 21 years of biologically effective dose. *Br J Radiol*. 2010 Jul;83(991):554-68.
16. Park C, Papiez L, Zhang S, Story M, Timmerman RD. Universal survival curve and single fraction equivalent dose: useful tools in understanding potency of ablative radiotherapy. *Int J Radiat Oncol Biol Phys*. 2008 Mar 1;70(3):847-52.
17. Herbert D. The assessment of the clinical significance of non-compliance with prescribed schedules of irradiation. *Int J Radiat Oncol Biol Phys*. 1977 Jul-Aug;2(7-8):763-72.
18. Jackson A, Ten Haken RK, Robertson JM, Kessler ML, Kutcher GJ, Lawrence TS. Analysis of clinical complication data for radiation hepatitis using a parallel architecture model. *Int J Radiat Oncol Biol Phys* 1995;31(4):883-91.
19. Cox DR, Snell EJ. *Analysis of binary data*. 2nd Ed. London: Chapman & Hall/CRC; 1989.
20. Levegrün S, Jackson A, Zelefsky MJ, Skwarchuk MW, Venkatraman ES, Schlegel W, Fuks Z, Leibel SA, Ling CC. Fitting tumor control probability models to biopsy outcome after three-dimensional conformal radiation therapy of prostate cancer: pitfalls in deducing radiobiologic parameters for tumors from clinical data. *Int J Radiat Oncol Biol Phys*. 2001;51:1064-80.
21. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS, March 31, 2003 (<http://ctep.cancer.gov>), Publish date; August 9 2006.
22. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 4.0, DCTD, NCI, NIH, DHHS, December 23, 2009 (<http://ctep.cancer.gov>), Publish date; May 28, 2009.
23. LENT SOMA scales for all anatomic sites. *Int J Radiat Oncol Biol Phys* 1995; 31:1049–1091.
24. Fehlaue F, Tribius S, Holler U, et al. Long-term radiation sequelae after breast-conserving therapy in women with early-stage breast cancer: an observational study using the LENT-SOMA scoring system. *Int J Radiat Oncol Biol Phys* 2003;55:651–8.
25. Fisher RA. On the Interpretation of χ^2 from Contingency Tables, and the Calculation of P. *Journal of the Royal Statistical Society*. 1922;85:87.
26. Kondziolka D. Current and novel practice of stereotactic radiosurgery. *J Neurosurg*. 2019 Jun 1;130(6):1789-1798.
27. Depp JG. Personal Communication, Founding President and CEO, Accuray Incorporated. Accessible via <http://quantum.site.nfoservers.com/Joe/>

28. Mahadevan A, Moningi S, Grimm J, Li XA, Forster KM, Palta M, Prior P, Goodman KA, Narang A, Heron DE, Lo SS, Urbanic J, Herman JM. Maximizing Tumor Control and limiting complications with SBRT for Pancreatic Cancer. **Int J Radiat Oncol Biol Phys**. HyTEC Special Issue. [In Review]
29. Holmes G. Some experiments in standardization of dosage for Roentgen therapeutics. *Am J Röntgenol*. 1914;1:298–302.
30. Quimby EH, Pack GT. The skin erythema for combinations of gamma and Roentgen rays. *Radiology* 13: 306, 1929. [Read by Mrs. Edith H. Quimby before the Radiological Society of North America at the Fourteenth Annual Meeting, at Chicago, Dec. 3-7: 1928.]
31. Taylor LS. History of the international commission on radiological units and measurements (ICRU). *Health Phys*. 1958 Dec;1(3):306-14.
32. Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constone LS, Eisbruch A, Bentzen SM, Nam J, Deasy JO. Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys*. 2010 Mar 1;76(3 Suppl):S10-9.
33. Svensson H, Westling P, Larsson LG. Radiation-induced lesions of the brachial plexus correlated to the dose-time-fraction schedule. *Acta Radiol Ther Phys Biol*. 1975 Jun;14(3):228-38.
34. Yan M, Kong W, Kerr A, Brundage M. The radiation dose tolerance of the brachial plexus: A systematic review and meta-analysis. *Clin Transl Radiat Oncol*. 2019 Jun 14;18:23-31.
35. Kong FM, Ritter T, Quint DJ, Senan S, Gaspar LE, Komaki RU, Hurkmans CW, Timmerman R, Bezjak A, Bradley JD, Movsas B, Marsh L, Okunieff P, Choy H, Curran WJ Jr. Consideration of dose limits for organs at risk of thoracic radiotherapy: atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. *Int J Radiat Oncol Biol Phys*. 2011 Dec 1;81(5):1442-57.
36. Li CH, Wu VW, Chiu G. A dosimetric evaluation on applying RTOG-based and CT/MRI-based delineation methods to brachial plexus in radiotherapy of nasopharyngeal carcinoma treated with helical tomotherapy. *Br J Radiol*. 2019 Oct;92(1102):20170881.
37. Ma TM, Emami B, Grimm J, Xue J, Asbell SO, Kubicek GJ, Lanciano R, Welsh JS, Peng L, Gui C, Das IJ, Goldman HW, Brady LW, Redmond KJ, Kleinberg LR. Volume Effects in Radiosurgical Spinal Cord Dose Tolerance: How Small is Too Small? *J Radiat Oncol*. 2019 Mar;8:53-61.
38. Peng L, Grimm J, Gui C, Shen CJ, Redmond KJ, Sloan L, Hazell S, Moore JA, Huang E, Spoletti N, Laub W, Quon H, Bettegowda C, Lim M, Kleinberg LR. Updated Risk Models Demonstrate Low Risk of Symptomatic Radionecrosis Following Stereotactic Radiosurgery for Brain Metastases in the Modern Era. *Surg Neurol Int*. 2019 Mar;10:32.

Figures

Probit Model of Grade 2-4 Brachial Plexopathy

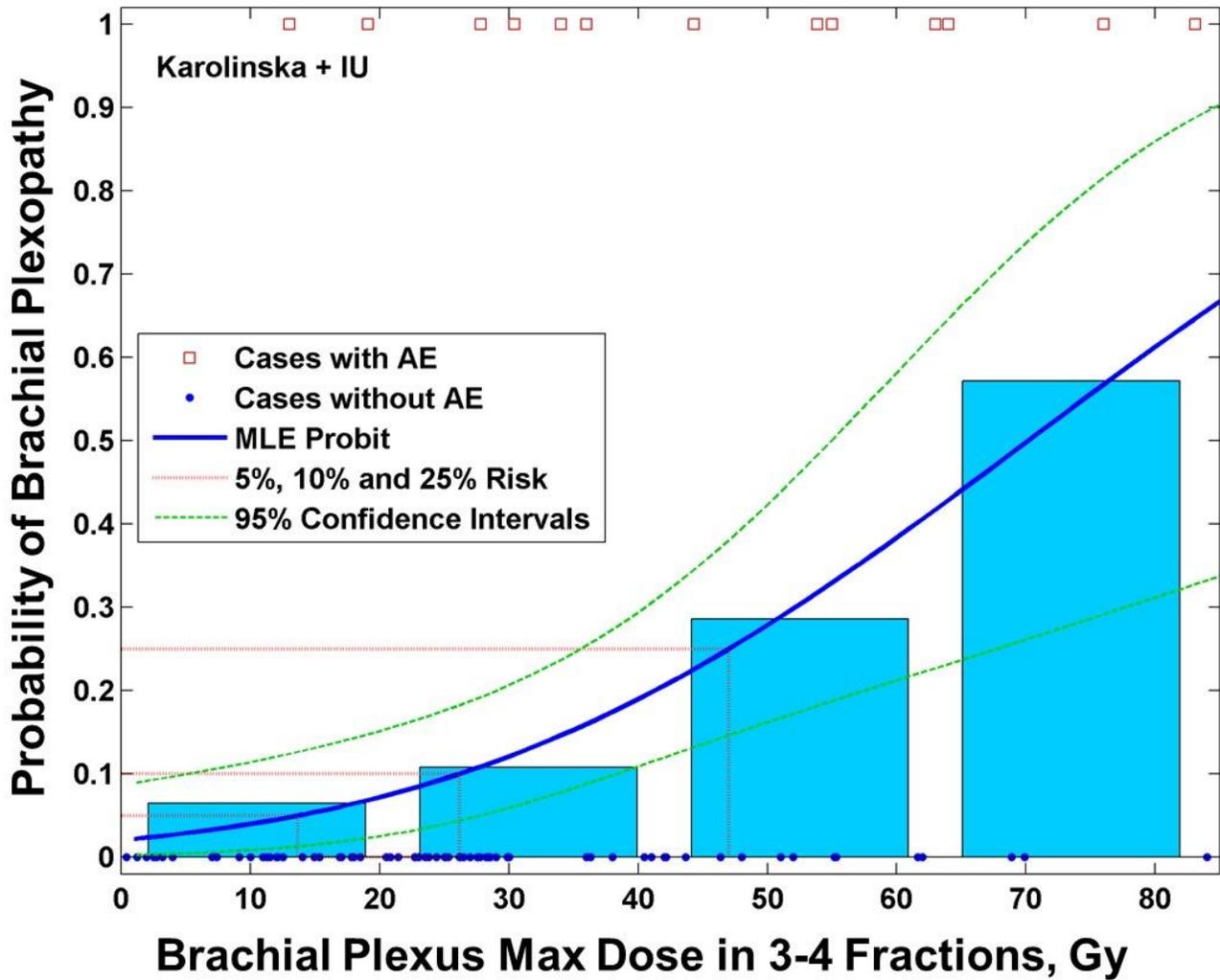
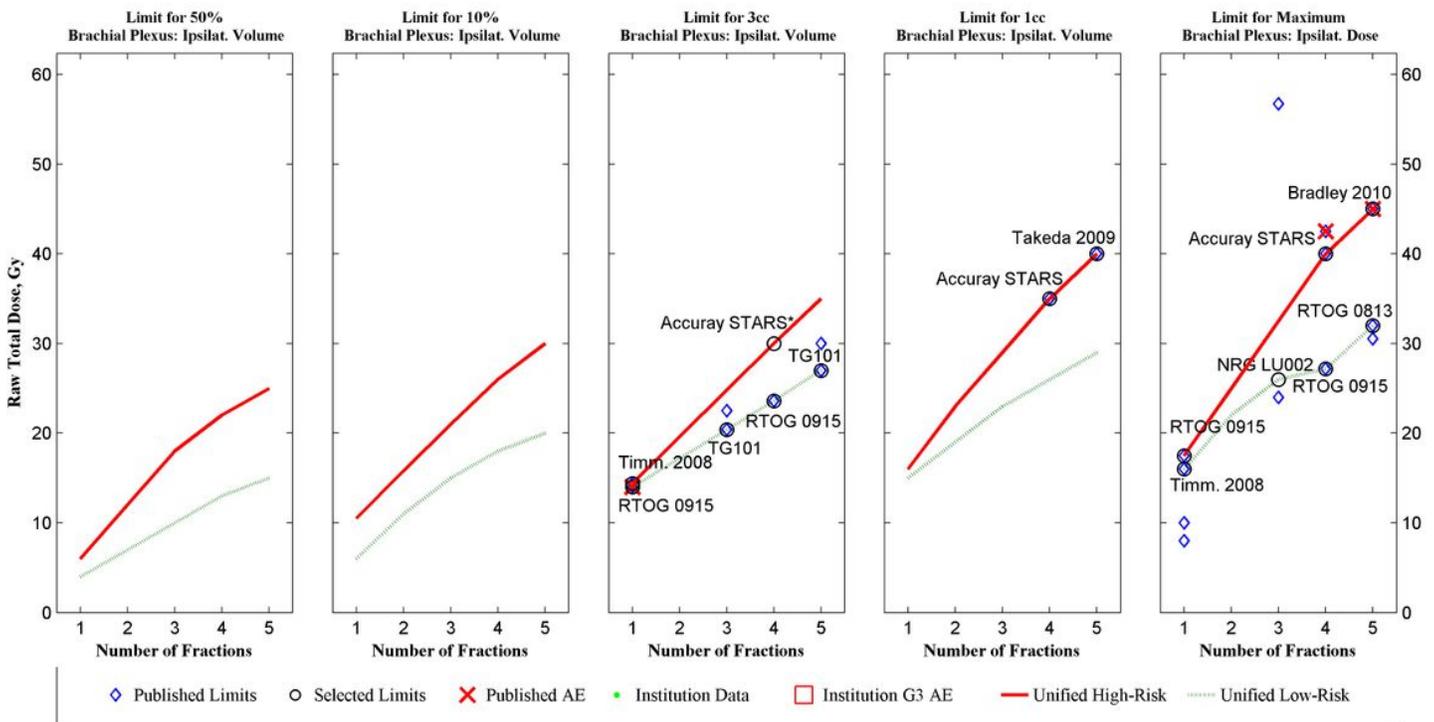


Figure 1

The Probit model (17) of Grade 2-4 Brachial Plexopathy shows the Dmax values of the two datasets (1, 2) with red squares denoting the cases corresponding to CTCAE grade 2 or higher adverse events (AE) and blue dots representing the cases without AE. According to the model, the risk of a BP with the dose of 26 Gy in 3-4 fractions is 10%, whereas the risk is 25% corresponded to 47Gy and 50% risk with a dose 70 Gy in 3 -4 fractions.



	Low Risk Limits					High Risk Limits				
	D50% Limit (Gy)	D10% Limit (Gy)	D3cc Limit (Gy)	D1cc Limit (Gy)	Dmax Limit (Gy)	D50% Limit (Gy)	D10% Limit (Gy)	D3cc Limit (Gy)	D1cc Limit (Gy)	Dmax Limit (Gy)
1 fx	4.0	6.0	14.0	15.0	16.0	6.0	10.5	14.4	16.0	17.5
2 fx	7.0	11.0	17.2	19.0	22.0	12.0	15.8	19.6	23.0	25.0
3 fx	10.0	15.0	20.4	23.0	26.0, 9.9%	18.0	21.0	24.8	29.0	32.5, 13.6%
4 fx	13.0	18.0	23.6	26.0	27.2, 9.0%	22.0	26.0	30.0	35.0	40.0, 15.5%
5 fx	15.0	20.0	27.0	29.0	32.0	25.0	30.0	35.0	40.0	45.0

Figure 2

DVH Risk Map for brachial plexus. Note that NRG LU-002 protocol has adopted the Dmax = 26 Gy in 3 fraction constraint from Forquer 2009 (1), which we have designated as the low-risk limit for Dmax in 3 fractions.

Number	NAME	DIAGNOSIS	Number of Treatments	Duration of Treatment	Average voltage used in kilovolts	Average number of milliamperes (min) given at each sitting	Total dosage received in milli-amperes (min)	Dose received before a reaction obtained	REMARKS
1	Mr. B	Epithelioma of 3rd finger, right hand	2	28 ds.	50	25	50	...	Improved.
2	Mr. B	Epithelioma, left side face	5	5 mo.	60	12	Cured.
3	Miss B	Carc Breast	14	6 mo.	60	25	Did not return.
4	Mr. B	Giant cell sarcoma tibia	14	8 mo.	70	50	Improved.
5	Mrs. C	Carc Breast	21	2 mo.	60	30	Did not return.
.
.
.
140	M. A	Lupus	5	5 wk.	60	20	102	102	Rather severe reaction.
.
.
.
196	Mrs. C. E. W . .	Epithelioma	15	17 mo.	50	25	Improved.
197	R. H. W	Epith Lip.	2	1 wk.	50	25	Improved.

Figure 3

Excerpt of an example de-identified published database from 1914, “Some Experiments in Standardization of Dosage” (29). Although precision is limited since this table pre-dates the definition of the rad by 4 decades (31) and was long before any of the modern grading systems (4), nevertheless the sharing of fractionation, multiple parameters of dose, and outcome per patient as still recommended by HyTEC and QUANTEC (39-40) is truly remarkable, since this dataset of 197 cases is from more than 100 years ago.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [NTCPNerveBrachialPlexusAppendix.doc](#)