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FULL PAPER

A dosimetric parameter to limit chest wall toxicity in SABR of NSCLC

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Objective: Chest wall (CW) toxicity (rib fracture and/or pain) is a recognized complication of stereotactic ablative radiotherapy (SABR) for non-small-cell lung cancer. The aim of this study was to evaluate the frequency of CW toxicity following SABR and to propose a new dosimetric parameter.

Methods: We reviewed the charts and SABR plans from patients treated for T1–T2N0 peripheral non-small-cell lung cancer between 2009 and 2015. The CW structure was created through a 3-cm expansion of the lung. The median dose delivered to the planning target volume was 60 Gy. SABR was delivered in three fractions for patients with CW $V_{30} < 30 \text{ cm}^3$. If the CW V_{30} exceeded 30 cm^3 , five fractions were used, and the plan was optimized based on CW V_{37} (biologically equivalent to the V_{30} of three-fraction plans).

Results: In 6 years, 361 lesions from 356 patients were treated (3 fractions: 297; 5 fractions: 64). The median follow-up was 16 months. 23 patients (6.5%) developed CW toxicity after a median time of 10 months following treatment. The mean CW V_{30}/V_{37} was 21 cm^3 for patients with CW toxicity and 17 cm^3 for patients without toxicity ($p < 0.05$). The 2-year local control and the CW toxicity rates were similar, whether patients received three or five fractions (97% vs 96% and 7% vs 5%).

Conclusion: When the CW V_{30} is $> 30 \text{ cm}^3$, altered fractionation combined with V_{37} optimization can limit CW toxicity.

Advances in knowledge: The CW V_{37} is a suggested dosimetric parameter adapted to fractionation that may potentially limit CW toxicity after lung SABR.

INTRODUCTION

Stereotactic ablative radiotherapy (SABR) is now a well-accepted option in the management of early-stage non-small-cell lung cancer (NSCLC) for patients who are medically unfit or who refuse surgery.^{1–3} SABR is highly effective with a low incidence of acute and late toxicity.^{4–10} Chest wall toxicity (CWT), defined as chest wall (CW) pain or rib fracture (symptomatic or not), is a recognized potential adverse effect of SABR. Although CWT is not life threatening, it can lead to severe and chronic pain that can dramatically affect the long-term quality of life of patients who have otherwise been cured of their early-stage cancer.

To reduce the incidence of CWT, models have been developed and dosimetric constraints have been defined for specific anatomical structures. In some studies,^{11–16} the CW was identified as a critical structure that corresponded to a 2- to 3-cm volumetric lung expansion from which the lung is subtracted. Dunlap et al¹¹ and Mutter et al¹² reported that the CW volume receiving 30 Gy is a major predictive parameter of CWT. In other studies,^{17–20} individual ribs were used as critical structures. For example, Petterson et al²⁰

showed that the risk for radiation-induced rib fracture was related to the dose received by 2 cm^3 of the rib structure. Finally, in the report of the American Association of Physicists in Medicine on SABR, both structures (CW and rib) were identified as useful organs at risk and the choice was left to the treating physician.

We have retrospectively reviewed a large cohort of early-stage NSCLC patients treated with SABR at our centre, assessing treatment outcomes and toxicities. The aim of this study was to determine the rate of CWT after SABR for NSCLC when applying current CW constraints and to validate an institutional dosimetric parameter for five-fraction regimens. We also evaluated two separate organs at risk, namely the CW and the rib, in order to determine the structure that best predicted for CWT.

METHODS AND MATERIALS

Patient and tumour selection

We reviewed patients treated with SABR for peripheral T1–T2N0 NSCLC at our institution between 2009 and 2015. This study was approved by our institutional review

board and ethics committee and conducted in accordance with the Canadian regulatory requirements. Patients with previous thoracic irradiation were excluded. Central lesions, defined as a tumour within 2 cm of the proximal tracheobronchial tree or that are adjacent to the mediastinum,²¹ were excluded. Histological confirmation had been sought, whenever possible, through bronchoscopy or transthoracic needle biopsy. When appropriate, gold fiducials were placed at the time of the percutaneous lung biopsy to allow tumour tracking. In the absence of histological confirmation (if biopsy was not feasible or was inconclusive), radiological and clinical criteria for probable neoplasia were used.²² Patients with repeated SABR treatments within the same lobe were excluded.

Treatment planning and delivery

SABR was delivered using robotic radiotherapy (CyberKnife®; Accuray Inc., Sunnyvale, CA) or isocentric linear accelerators with volumetric arc therapy (VMAT). All patients had a non-contrast four-dimensional planning CT scan in the supine position. Patients were treated either with near-real-time tumour tracking with CyberKnife or using an internal target volume (ITV).

For patients treated with CyberKnife, tumour tracking was achieved using one of three methods: fiducials; soft-tissue tracking (Xsight® Lung; Accuray Inc., Sunnyvale, CA)²³ when tumours were sufficiently large and dense; and using an ITV (based on four-dimensional CT scan motion) associated with the tracking of adjacent vertebrae (Xsight Spine®).²⁴ For dose calculation, the Ray-Tracing algorithm was used prior to 2012 and was replaced by the Monte-Carlo algorithm thereafter.²⁵

For patients treated with VMAT, a BodyFix (Elekta™, Crawley, UK) whole-body vacuum immobilization device was used. The ITV was based on tumour motion in extreme phases of the respiratory cycle and the analytical anisotropic algorithm was used for dose calculation.

For both techniques, an additional planning tumour volume (PTV) margin of 5 mm was added to the ITV.

Chest wall and ribs

Since 2010, all patients treated at the Centre Hospitalier de l'Université de Montréal had an optimization on the CW structure. The CW structure was defined as a 3-cm expansion of the ipsilateral lung excluding the lung itself. The CW volume receiving 30 Gy was limited to 30 cm³ ($V_{30} < 30 \text{ cm}^3$).¹¹ For patients treated before 2010, this structure was delineated retrospectively, and all patients respected this constraint.

The dose to the rib structure was not evaluated in our routine practice. The rib structure was thus retrospectively delineated on all SABR plans included in this study.

Dose schedules and constraints

The prescribed dose to the PTV was 60 Gy. SABR was delivered in three fractions for patients with CW $V_{30} < 30 \text{ cm}^3$. If the CW $V_{30} > 30 \text{ cm}^3$, five fractions were delivered and the SABR plan was optimized to deliver a CW V_{37} of $< 30 \text{ cm}^3$. Because SABR

was delivered in three or five fractions, dose values were expressed in biologically equivalent dose. For the prescribed dose an alpha/beta ratio of 10 Gy was used and the dose was expressed in Gy₁₀. For organs at risk, the biologically equivalent dose was expressed in Gy₃ using an alpha/beta ratio of 3 Gy for late responding tissues.^{26,27}

The V_{37} was calculated to be biologically equivalent to the CW V_{30} at three fractions: 130 Gy₃. In addition, other CW dosimetric parameters were assessed: the V_{50} , the maximal dose (D_{max}), the dose received by 1 cm³ ($D_{1\text{cc}}$) and the shortest distance between the CW and the edge of the ITV. We also documented the dose received by 1 cm³ of the rib structure. These values were then compared with common dosimetric values used to limit rib doses: $D_{1\text{cc}} < 28.8 \text{ Gy}$ for three-fractions treatment and $D_{1\text{cc}} < 35 \text{ Gy}$ for five-fractions treatment.²⁸

Follow-up and end points

After completion of SABR, patients were first seen at 2–3 months for a detailed history and physical examination, and every 6 months thereafter. A chest CT scan was performed before each visit.

The primary end point was the frequency and severity of CWT evaluated by physicians based on the pain scale of the Common Terminology Criteria for Adverse Events v. 4.0. Only patients with CW pain more than equal to grade 2 were considered for analysis. Patients whose toxicity level changed during follow-up were scored at the time of greatest toxicity. A secondary end point was to validate an institutional dosimetric parameter (CW V_{37}) for patients with CW $V_{30} > 30 \text{ cm}^3$. Local control and rib fracture were determined on follow-up CTs. Local control was defined by the absence of growing lesion within the involved lobe.²⁹

Table 1. Patient and tumour characteristics, presented as mean and range

Patients	N = 356
Age (years)	74 (44–94)
Sex (male/female)	198/158
KPS (%)	80 (40–100)
FEV1 (L)	1.4 (0.5–3.5)
FEV1 (% predicted)	63.8 (16–172)
DLCO (% predicted)	57 (11–128)
Lesions	N = 361
Size (cm)	1.9 (0.6–5.0)
Histological confirmation	68%
Adenocarcinoma	37%
Squamous cell carcinoma	21%
Large cell carcinoma	3%
Other specified carcinoma	7%

DLCO, carbon monoxide lung diffusion capacity; FEV1 (L), forced expiratory volume (in liter) in 1 s; KPS, Karnofsky prognostic status.

Statistics

Statistical analysis was performed by SPSS® v. 24.0 software (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). The local control was estimated using the Kaplan–Meier method. Data were collected and analyzed using Student's *t*-test, χ^2 and Fisher's exact test. *p*-values <0.05 were considered statistically significant.

RESULTS

Between July 2009 and August 2015, 361 treatments were delivered (55% with CyberKnife and 45% with VMAT) in 356 patients. Among the 361 treatments, 297 (82%) received 60 Gy in 3 fractions (180 Gy₁₀) and 64 (18%) received 60 Gy in 5 fractions (132 Gy₁₀). Patient characteristics are summarized in Table 1.

The mean CW V_{30}/V_{37} was 21 cm³ for patients with CW toxicity and 17 cm³ for patients without toxicity (*p* = 0.04). In the three-fractions group, the CW V_{30} for patients with CWT was 21 cm³, whereas it was 15 cm³ for patients without CWT (*p* = 0.012). In the five-fractions group, the CW V_{37} was 25 cm³ in patients with CWT and 23 cm³ in patients without CWT (*p* > 0.1). The Rib D_{max} and the CW D_{max} were also significantly different between the CWT group and the no-CWT group: 522 vs 401 Gy₃ (*p* = 0.04) and 580 vs 486 Gy₃ (*p* = 0.01). The D_{1cc} constraint on the retrospectively drawn rib was exceeded in >80% of SABR plans. The mean rib D_{1cc} was 283 Gy₃ in the group with CWT vs 227 Gy₃ in the group without toxicity (*p* > 0.1). CWT in patients respecting the rib D_{1cc} was 4% vs 7% in patients that exceeded this constraint (*p* > 0.1). Patients with CWT had tumours closer to the CW than those without CWT (2.6 vs 6.0 mm, *p* = 0.02). Results are presented in Table 2.

Among all patients, 23 patients (6.5%) had CWT (20 patients in the 3-fractions group and 3 patients in the 5-fractions group).

12 patients (3.4%) developed rib fractures and 20 patients (5.6%) presented with CW pain (grade 2: 90%; grade 3: 10%) (Figure 1). CWT was reported after a median time of 10 months (range, 2–41 months) following treatment. The CWT rate was 7% for patients receiving 180 Gy₁₀ vs 5% for patients who received 132 Gy₁₀ (*p* > 0.1). The CWT rate for patients treated with tumour tracking (fiducials and Xsight Lung) was equivalent to the CWT rate of patients treated without tumour tracking (7.8% vs 5.9%, *p* > 0.1). No statistically significant differences were found when analyzing rib fractures separately.

The median follow-up was 16 months (1–62 months). The 2-year local control was 97% for patients receiving 180 Gy₁₀ vs 96% for patients who received 132 Gy₁₀ (*p* > 0.1).

DISCUSSION

In this large cohort, we have demonstrated that the CWT rate after SABR for NSCLC is as low as 6.5% when CW V_{30} constraints are used. By contrast, initial studies that determined the need for specific CW constraints reported higher rates of CWT reaching up to 30%.^{11,16,30,31} However, in these studies, patients were treated without constraints on the CW. Stephans et al,³¹ in a retrospective study, suggested that applying CW constraints should limit the incidence of CWT to 10–15%. Our CWT rate is comparable to that seen in the study by Coroller et al³² which reported a 9.7% rate of CWT ($\geq$ grade 2) and also used a risk-adapted approach with three or five fractions depending on the CW V_{30} .

The CW V_{30} seems to be the best predictive parameter of CWT as suggested by several studies.^{11,12} In our study, the mean CW V_{30} was significantly higher in the group with CWT. In addition, the distance between the edge of the tumour and the CW is also an important factor to consider. Our results confirm that patients with CWT have tumours closer to the CW. This is also

Table 2. Dosimetric parameters (mean values)

Dosimetric Parameters	CWT (<i>n</i> = 23)	No CWT (<i>n</i> = 338)	Range	<i>p</i> -value
Tumour size (cm)	1.9	2	0.6–3.9	NS
CW parameters				
V_{30}/V_{37} (cm ³)	21	17	0–30	0.04
D_{max} (Gy ₃)	580	486	78–862	0.01
V_{50} (cm ³)	3.6	3.3	0–61	NS
D_{1cc} (Gy ₃)	411	338	9–718	0.05
Rib parameters				
D_{max} (Gy ₃)	522	401	22–810	0.04
V_{50} (cm ³)	1	1	0–54	NS
D_{1cc} (Gy ₃)	283	227	1–588	NS
ITV-CW distance (mm)	2.6	6	0–37	0.02
Technique: CyberKnife®/VMAT	13/10	187/151		NS
Tumour tracking: yes/no	12/11	153/185		NS

CW, chest wall; CWT, chest wall toxicity; D_{max} , maximal dose; Gy₃, dose expressed in biological equivalent dose for an alpha/beta ratio of 3 Gy; ITV, internal target volume; NS, non significant; V_n , volume of a structure receiving *n* Gy; VMAT, volumetric modulated arc-therapy.

Figure 1. Chest wall (CW) toxicity repartition in the whole cohort.

congruent with the findings of Andolino et al¹³ who showed an increase of the frequency of CWT for lesions for which the 50% isodose line abutted the CW (21% vs 4%, $p < 0.0001$). Unsurprisingly, the $D_{\max}$ (CW and rib) was higher in the CWT group and was correlated with the distance to the CW. Other proposed dosimetric parameters (D_{1cc} Rib, V_{50} Rib and V_{50} CW) were not statistically significant in our cohort.

The use of a broad CW structure can be surprising in the realm of SABR where constraints are defined on small volumes of organs at risk. This is probably why some studies used individual ribs as organs at risk. In our study, proposed constraints on rib structures (D_{1cc}) were exceeded in many cases without leading to clinical toxicity. Potential reasons explaining these findings include the fact that tumour motion in relation to the rib, which may decrease the hot spot, is not taken into account in our dosimetry. Also, intercostal irradiation may contribute to toxicity.

Although increased fractionation has already been shown to be a good option to reduce CWT,³² our study shows that a new dosimetric parameter, CW V_{37} , can be used to limit CWT. For patients with CW $V_{30} > 30 \text{ cm}^3$, the number of fractions

delivered was increased from three to five, and their SABR plans were also optimized on the CW V_{37} . As the CWT rate is similar between our patients who received 180 or 132 Gy₁₀, it seems that an altered fractionation treatment combined to a CW V_{37} optimized treatment is a good alternative to limit the CWT for patients with CW V_{30} exceeding 30 cm^3 . This is probably because fractionation leads to a major dose reduction to late responding tissues.

The low CWT rate supports our decision to keep the same dose schedule as in the Radiation Therapy Oncology Group 0236⁸ rather than lower dose schedules as used in other trials,³³ regardless of which treatment-planning algorithm was used. Several studies, including a previously published study by our institution,²³ used this approach and reported similar results in terms of outcomes and toxicities.^{8,34–36} In a previous study, we showed that no significant differences were found after recalculation with heterogeneity correction in CW V_{30} .³⁷ PTV dose reduction does not seem to be necessary to reduce toxicities, including CWT.

The main limitations of our study are its retrospective nature and the low number of events, but this is the largest cohort that evaluates CWT applying CW constraints. Although CWT toxicity peaks at 10 months post-treatment, our median follow-up period of 16 months may also be a limitation. Other dosimetric parameters (D_{1cc} rib, V_{50} rib and V_{50} CW) could have been significant but our small study may have been underpowered to adequately evaluate these factors. Although the CW V_{37} is issued from the linear-quadratic model and its inherent limitations at large dose per fraction, this assumption seems reasonable considering the results of the five-fraction cohort. This study assess that V_{30}/V_{37} is correlated to CWT and introduces the parameter of CW V_{37} to optimize SABR plans for patients with CW $V_{30} > 30 \text{ cm}^3$.

CONCLUSION

The CWT rate after SABR for NSCLC is low when applying adapted CW constraints. Despite the small number of events, we found that CW V_{30}/V_{37} is significantly associated to CWT. When the CW V_{30} is $> 30 \text{ cm}^3$, altered fractionation combined with V_{37} optimization can limit CWT without compromising tumour control.

REFERENCES

1. Ettinger DS, Akerley W, Bepler G, Blum MG, Chang A, Cheney RT, et al. Non-small cell lung cancer. *J Natl Compr Canc Netw* 2010; **8**: 740–801.
2. Louie AV, Palma DA, Dahele M, Rodrigues GB, Senan S. Management of early-stage non-small cell lung cancer using stereotactic ablative radiotherapy: controversies, insights, and changing horizons. *Radiother Oncol* 2015; **114**: 138–47. doi: <https://doi.org/10.1016/j.radonc.2014.11.036>
3. Murray P, Franks K, Hanna GG. A systematic review of outcomes following stereotactic ablative radiotherapy in the treatment of early-stage primary lung cancer. *Br J Radiol* 2017; **90**: 20160732.
4. Onishi H, Araki T, Shirato H, Nagata Y, Hiraoka M, Gomi K, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. *Cancer* 2004; **101**: 1623–31. doi: <https://doi.org/10.1002/cncr.20539>
5. Grills IS, Mangona VS, Welsh R, Chmielewski G, McNerney E, Martin S, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. *J Clin Oncol* 2010; **28**: 928–35. doi: <https://doi.org/10.1200/jco.2009.25.0928>
6. Senthil S, Lagerwaard FJ, Haasbeek CJ, Slotman BJ, Senan S. Patterns of disease

- recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. *Lancet Oncol* 2012; **13**: 802–9. doi: [https://doi.org/10.1016/s1470-2045\(12\)70242-5](https://doi.org/10.1016/s1470-2045(12)70242-5)
7. Baumann P, Nyman J, Hoyer M, Wennberg B, Gagliardi G, Lax I, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. *J Clin Oncol* 2009; **27**: 3290–6. doi: <https://doi.org/10.1200/jco.2008.21.5681>
 8. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010; **303**: 1070–6. doi: <https://doi.org/10.1001/jama.2010.261>
 9. Brada M, Pope A, Baumann M. SABR in NSCLC—the beginning of the end or the end of the beginning? *Radiother Oncol* 2015; **114**: 135–7. doi: <https://doi.org/10.1016/j.radonc.2015.01.012>
 10. Nyman J, Hallqvist A, Lund JÅ, Brustugun OT, Bergman B, Bergström P, et al. SPACE—a randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. *Radiother Oncol* 2016; **121**: 1–8.
 11. Dunlap NE, Cai J, Biedermann GB, Yang W, Benedict SH, Sheng K, et al. Chest wall volume receiving >30 Gy predicts risk of severe pain and/or Rib fracture after lung stereotactic body radiotherapy. *Int J Radiat Oncol* 2010; **76**: 796–801. doi: <https://doi.org/10.1016/j.ijrobp.2009.02.027>
 12. Mutter RW, Liu F, Abreu A, Yorke E, Jackson A, Rosenzweig KE. Dose–volume parameters predict for the development of chest wall pain after stereotactic body radiation for lung cancer. *Int J Radiat Oncol* 2012; **82**: 1783–90. doi: <https://doi.org/10.1016/j.ijrobp.2011.03.053>
 13. Andolino DL, Forquer JA, Henderson MA, Barriger RB, Shapiro RH, Brabham JG, et al. Chest wall toxicity after stereotactic body radiotherapy for malignant lesions of the lung and liver. *Int J Radiat Oncol* 2011; **80**: 692–7. doi: <https://doi.org/10.1016/j.ijrobp.2010.03.020>
 14. Bongers EM, Haasbeek CJ, Lagerwaard FJ, Slotman BJ, Senan S. Incidence and risk factors for chest wall toxicity after risk-adapted stereotactic radiotherapy for early-stage lung cancer. *J Thorac Oncol* 2011; **6**: 2052–7. doi: <https://doi.org/10.1097/jto.0b013e3182307e74>
 15. Creach KM, El Naqa I, Bradley JD, Olsen JR, Parikh PJ, Drzymala RE, et al. Dosimetric predictors of chest wall pain after lung stereotactic body radiotherapy. *Radiother Oncol* 2012; **104**: 23–7. doi: <https://doi.org/10.1016/j.radonc.2012.01.014>
 16. Woody NM, Videtic GM, Stephans KL, Djemil T, Kim Y, Xia P. Predicting chest wall pain from lung stereotactic body radiotherapy for different fractionation schemes. *Int J Radiat Oncol* 2012; **83**: 427–34. doi: <https://doi.org/10.1016/j.ijrobp.2011.06.1971>
 17. Kim SS, Song SY, Kwak J, Ahn SD, Kim JH, Lee JS, et al. Clinical prognostic factors and grading system for rib fracture following stereotactic body radiation therapy (SBRT) in patients with peripheral lung tumors. *Lung Cancer* 2013; **79**: 161–6. doi: <https://doi.org/10.1016/j.lungcan.2012.10.011>
 18. Welsh J, Amini A, Ciura K, Nguyen N, Palmer M, Soh H, et al. Evaluating proton stereotactic body radiotherapy to reduce chest wall dose in the treatment of lung cancer. *Med Dosim* 2013; **38**: 442–7. doi: <https://doi.org/10.1016/j.meddos.2013.08.001>
 19. Welsh J, Thomas J, Shah D, Allen PK, Wei X, Mitchell K, et al. Obesity increases the risk of chest wall pain from thoracic stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 2011; **81**: 91–6. doi: <https://doi.org/10.1016/j.ijrobp.2010.04.022>
 20. Pettersson N, Nyman J, Johansson KA. Radiation-induced rib fractures after hypofractionated stereotactic body radiation therapy of non-small cell lung cancer: a dose- and volume-response analysis. *Radiother Oncol* 2009; **91**: 360–8. doi: <https://doi.org/10.1016/j.radonc.2009.03.022>
 21. Timmerman R, McGarry R, Yiannoutsos C, Papiez L, Tudor K, DeLuca J, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006; **24**: 4833–9. doi: <https://doi.org/10.1200/jco.2006.07.5937>
 22. Gould MK, Fletcher J, Iannettoni MD, Lynch WR, Midthun DE, Naidich DP, et al. Evaluation of patients with pulmonary nodules: when is it lung cancer?: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007; **132**(Suppl. 3): 108S–30.
 23. Bahig H, Campeau MP, Vu T, Doucet R, Béliveau Nadeau D, Fortin B, et al. Predictive parameters of CyberKnife fiducial-less (XSight Lung) applicability for treatment of early non-small cell lung cancer: a single-center experience. *Int J Radiat Oncol Biol Phys* 2013; **87**: 583–9. doi: <https://doi.org/10.1016/j.ijrobp.2013.06.2048>
 24. Fu D, Kahn R, Wang B, Wang H, Mu Z, Kuduvalli G, et al. Fiducial-free lung tumor tracking for CyberKnife radiosurgery. *Int J Radiat Oncol Biol Phys* 2008; **72**: S608–9. doi: <https://doi.org/10.1016/j.ijrobp.2008.06.235>
 25. Okoye CC, Patel RB, Hasan S, Podder T, Khouri A, Fabien J, et al. Comparison of ray tracing and Monte Carlo calculation algorithms for thoracic spine lesions treated with CyberKnife-based stereotactic body radiation therapy. *Technol Cancer Res Treat* 2016; **15**: 196–202. doi: <https://doi.org/10.1177/1533034614568026>
 26. Dale RG. The application of the linear-quadratic dose-effect equation to fractionated and protracted radiotherapy. *Br J Radiol* 1985; **58**: 515–28. doi: <https://doi.org/10.1259/0007-1285-58-690-515>
 27. Bentzen SM, Dörr W, Gahbauer R, Howell RW, Joiner MC, Jones B, et al. Bioeffect modeling and equieffective dose concepts in radiation oncology—terminology, quantities and units. *Radiother Oncol* 2012; **105**: 266–8. doi: <https://doi.org/10.1016/j.radonc.2012.10.006>
 28. Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. *Med Phys* 2010; **37**: 4078–101. doi: <https://doi.org/10.1118/1.3438081>
 29. Huang K, Senthil S, Palma DA, Spoelstra FO, Warner A, Slotman BJ, et al. High-risk CT features for detection of local recurrence after stereotactic ablative radiotherapy for lung cancer. *Radiother Oncol* 2013; **109**: 51–7. doi: <https://doi.org/10.1016/j.radonc.2013.06.047>
 30. Lagerwaard FJ, Haasbeek CJ, Smit EF, Slotman BJ, Senan S. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2008; **70**: 685–92. doi: <https://doi.org/10.1016/j.ijrobp.2007.10.053>
 31. Stephans KL, Djemil T, Tendulkar RD, Robinson CG, Reddy CA, Videtic GM. Prediction of chest wall toxicity from lung stereotactic body radiotherapy (SBRT). *Int J Radiat Oncol Biol Phys* 2012; **82**: 974–80. doi: <https://doi.org/10.1016/j.ijrobp.2010.12.002>
 32. Coroller TP, Mak RH, Lewis JH, Baldini EH, Chen AB, Colson YL, et al. Low incidence of chest wall pain with a risk-adapted lung

- stereotactic body radiation therapy approach using three or five fractions based on chest wall dosimetry. *PLoS One* 2014; **9**: e94859.
33. Chang JY, Senan S, Paul MA, Mehran RJ, Louie AV, Balter P, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol* 2015; **16**: 630–7. doi: [https://doi.org/10.1016/s1470-2045\(15\)70168-3](https://doi.org/10.1016/s1470-2045(15)70168-3)
 34. Brown WT, Wu X, Fayad F, Fowler JF, García S, Monterroso MI, et al. Application of robotic stereotactic radiotherapy to peripheral stage I non-small cell lung cancer with curative intent. *Clin Oncol (R Coll Radiol)* 2009; **21**: 623–31. doi: <https://doi.org/10.1016/j.clon.2009.06.006>
 35. van der Voort van Zyp NC, Prévost JB, Hoogeman MS, Praag J, van der Holt B, Levendag PC, et al. Stereotactic radiotherapy with real-time tumor tracking for non-small cell lung cancer: clinical outcome. *Radiother Oncol* 2009; **91**: 296–300. doi: <https://doi.org/10.1016/j.radonc.2009.02.011>
 36. Davis JN, Medbery C, Sharma S, Pablo J, Kimsey F, Perry D, et al. Stereotactic body radiotherapy for centrally located early-stage non-small cell lung cancer or lung metastases from the RSSearch® patient registry. *Radiat Oncol* 2015; **10**: 113. doi: <https://doi.org/10.1186/s13014-015-0417-5>
 37. Bahig H, Filion E, Doucet R, Béliveau-Nadeau D, Vu T, Roberge D, et al. CyberKnife lung SBRT: from semi-homogeneous to Monte Carlo dose calculation. *J Radiosurg SBRT* 2013; **2**(Suppl. 2.1): 135–6.