International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

Incidental Prophylactic Nodal Irradiation and Patterns of Nodal Relapse in Inoperable Early Stage NSCLC Patients Treated With SBRT: A Case-Matched Analysis

Louis Lao, MBChB,*,† Andrew J. Hope, MD,* Manjula Maganti, MSc,‡ Anthony Brade, MD, PhD,* Andrea Bezjak, MD,* Elantholi P. Saibishkumar, MD,* Meredith Giuliani, MBBS,* Alexander Sun, MD,* and B. C. John Cho, MD, PhD*

**Department of Radiation Oncology, Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada; †Department of Radiation Oncology, Auckland City Hospital, Auckland, New Zealand; and ‡Department of Biostatistics, Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada*

Received Nov 8, 2013, and in revised form Apr 29, 2014. Accepted for publication May 5, 2014.

Summary

This nested, matched case-control study tested the hypothesis that incidental nodal irradiation during stereotactic body radiation therapy for early stage non-small cell lung cancer reduces the risk of nodal relapse. The analysis suggests that incidental hilar doses greater than 20 Gy are associated with fewer hilar relapses.

Purpose: Reported rates of non-small cell lung cancer (NSCLC) nodal failure following stereotactic body radiation therapy (SBRT) are lower than those reported in the surgical series when matched for stage. We hypothesized that this effect was due to incidental prophylactic nodal irradiation.

Methods and Materials: A prospectively collected group of medically inoperable early stage NSCLC patients from 2004 to 2010 was used to identify cases with nodal relapses. Controls were matched to cases, 2:1, controlling for tumor volume (ie, same or greater) and tumor location (ie, same lobe). Reference (normalized to equivalent dose for 2-Gy fractions [EQD2]) point doses at the ipsilateral hilum and carina, demographic data, and clinical outcomes were extracted from the medical records. Univariate conditional logistical regression analyses were performed with variables of interest.

Results: Cases and controls were well matched except for size. The controls, as expected, had larger gross tumor volumes ($P = .02$). The mean ipsilateral hilar doses were 9.6 Gy and 22.4 Gy for cases and controls, respectively ($P = .014$). The mean carinal doses were 7.0 Gy and 9.2 Gy, respectively ($P = .13$). Mediastinal nodal

Reprint requests to: B. C. John Cho, MD, PhD, Department of Radiation Oncology, Princess Margaret Cancer Centre 5-921, 610 University Ave, Toronto, ON M5G 2M9, Canada. Tel: (416) 946-2124; E-mail: john.cho@rmp.uhn.on.ca

This work was supported in part by the Princess Margaret Cancer Foundation, Department of Radiation Oncology Academic Enrichment Fund.

Presented at the 15th Annual World Conference on Lung Cancer, Sydney, Australia, Oct 27-30, 2013.

Conflict of interest: Some research funding for the stereotactic lung radiation therapy program at Princess Margaret Cancer Centre was provided by Elekta Synergy Research Group, Elekta Ltd., Crawley, UK.

Supplementary material for this article can be found at www.redjournal.org.

Int J Radiation Oncol Biol Phys, Vol. 90, No. 1, pp. 209–215, 2014
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2014.05.006

relapses, with and without ipsilateral hilar relapse, were associated with mean ipsilateral hilar doses of 3.6 Gy and 19.8 Gy, respectively ($P = .01$). The conditional density plot appears to demonstrate an inverse dose-effect relationship between ipsilateral hilar normalized total dose and risk of ipsilateral hilar relapse.

Conclusions: Incidental hilar dose greater than 20 Gy is significantly associated with fewer ipsilateral hilar relapses in inoperable early stage NSCLC patients treated with SBRT.

Introduction

Stereotactic body radiation therapy (SBRT) is a hypofractionated, conformal radiation treatment technique in which ablative doses are delivered using few fractions (typically 1-8) to an extracranial target, aided by image guidance (image-guided RT) to allow precise and accurate delivery of the dose prescribed. Several phase 1 and 2 studies have demonstrated the effectiveness of SBRT in treating early stage, node-negative non-small cell lung cancer (NSCLC) (1-5). Available evidence suggests that the results are comparable to those reported in the surgical series, although, to date, there has been no published randomized comparisons. In many centers, SBRT has become the treatment of choice for inoperable early stage NSCLC (6, 7). SBRT provides excellent local control with 2-year local control rates on the order of 90% or more, in significant contrast to conventional radiation therapy (8). Patterns of failure are predominantly nodal and distant with relapse rates of approximately 5% to 10% and 15% to 20%, respectively (2, 9).

Reported nodal failure rates for SBRT appear to be lower than those reported in the surgical series when matched for stage (10-14). We hypothesize that the lower nodal relapse rates observed in SBRT series are due to incidental hilar dose. We therefore compared the doses to mediastinum/hilum from SBRT treatment to the rates of nodal relapse based on a retrospective review of a cohort of 246 patients treated at Princess Margaret Cancer Centre.

Methods and Materials

Patients

A nested case-control study design was used to address the study question. Both the cases and controls were selected from a prospectively collected cohort of 246 consecutive patients treated with lung SBRT at our institution from 2004 to 2010. With approval from the research ethics board, a prospective database of all patients treated with lung SBRT at our institution was maintained since starting the lung SBRT program in 2004. This study is covered by the same ethics board approval. The database includes baseline patient characteristics, treatment parameters, and outcomes. Patients in the database were followed to the time of death according to protocol with regular follow-up and imaging. Follow-up computed tomography (CT) scans were performed routinely at 3, 6, 12, and 24 months posttreatment and annually until death after 2 years' follow-up. Chest X-rays are obtained at 9 and 18 months posttreatment. Additional imaging was performed only if indicated, based on patient symptoms and physical examinations. Nodal recurrences were determined by group consensus based on either radiological (progressive enlargement on serial scans) or biopsy results. Follow-up positron emission tomography (PET) scans were performed only if deemed helpful in clarifying management. Biopsy confirmation and salvage surgery were performed in selected cases, where appropriate. Death and cause of death were obtained from Cancer Care Ontario (Cancer Registry) and from local health providers if patients lived outside Ontario. Relevant clinical notes were requested from relevant sources, and the cause of death was determined by the treating physician.

Methodology

From the cohort of 246 lung SBRT patients, we excluded patients with metastatic disease to the lung from a nonlung primary; patients with evidence of regional or distant metastatic disease at the time of diagnosis; patients previously diagnosed with lung cancer treated within 3 years prior to SBRT; and patients presenting with more than 1 tumor within the lung. There were 179 patients remaining, of whom 19 patients who had nodal recurrence as their first site of failure were identified. We matched them to 38 controls from the same cohort without nodal failure at the time of censorship (Table 1).

The controls were matched to cases in a 2:1 ratio. The controls were manually matched to the cases based on tumor volume and location. To ensure there was no bias against the cases, we selected controls with larger tumors when tumors of the same volume could not be identified. The investigators were blinded to the dosimetric outcome (ie, dose to the mediastinum/ipsilateral hilum) at the time of matching. Care was taken in selecting controls with appropriate length of follow-up to account for the progression free period of the matching case.

Information collected included baseline patient characteristics including age, sex, T category, tumor location, gross tumor diameter (GTD), method of nodal staging, SUV_{max} value on PET and histology. Treatment parameters abstracted included gross tumor volume (GTV), planning target volume (PTV), and dose fractionation. Follow-up

Table 1 Patient demographics

Variable	Mean no. of patients ± SD with nodal relapse (%)	Mean no. of patients ± SD without nodal relapse (%)	*P* value
Total no. of patients	19	38	
Age	72 ± 8	75 ± 8	.19
Sex			.22
Female	8 (42.1)	22 (57.9)	
Male	11 (57.9)	16 (42.1)	
T-stage (collapsed categories)			.052
T1a	5 (26.3)	2 (5.3)	
T1b	4 (21.1)	6 (15.8)	
T2a	9 (47.4)	25 (65.8)	
T2b	1 (5.3)	5 (13.1)	
Location*			
LLL	4 (21.1)	8 (21.1)	
LUL	1 (5.3)	2 (5.3)	
RLL	2 (10.5)	4 (10.5)	
RML	2 (10.5)	4 (10.5)	
RUL	10 (52.6)	20 (52.6)	
GTD (cm)	3.0 ± 1.3	3.9 ± 1.01	.005
GTV (cm^3)	20.7 ± 23.3	28.3 ± 21.7	.02
Nodal staging*			
CT	0	6 (15.8)	
MED	0	1 (2.6)	
PET	16 (84.2)	27 (71.1)	
PET + EBUS	2 (10.5)	1 (2.6)	
PET + MED	1 (5.3)	3 (7.9)	
Histology (collapsed categories)			NS
Adenocarcinoma	5 (26.3)	12 (31.6)	
Squamous cell carcinoma	4 (21.1)	9 (23.7)	
Large cell carcinoma	1 (5.3)	3 (7.9)	
NSCLC NOS	4 (21.1)	6 (15.6)	
No Bx/Non-diagnostic	5 (26.3)	8 (21)	
Histology			.84
Adenocarcinoma	5 (26.3)	12 (31.6)	
Squamous cell carcinoma	4 (21.1)	9 (23.7)	
Other*	10 (52.6)	17 (44.7)	

Abbreviations: Bx = biopsy; CT = computer tomography; EBUS = endobronchial ultrasonography; GTD = gross tumor diameter; GTV = gross tumor volume; LLL = left lower lobe; LUL = left upper lobe; MED = mediastinoscopy; NOS = not otherwise specified; NS = non-significant; NSCLC = non-small cell lung cancer; PET = positron emission tomography; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe.

* Other includes large-cell carcinoma, NSCLC NOS, and no Bx or non-diagnostic.

data collected included time to death or last follow-up, disease status at last follow-up, and time to first relapse. For the cases, additional information about the extent of nodal involvement at the time of the first nodal relapse was collected based on nodal stations (15).

We derived the dosimetric data for each patient by retrieving their treatment plan from the treatment planning system (Pinnacle version 8.0 h; Philips, Fitchburg, WI) and adding 2 8-mm-diameter points of interest (POI) on the reference planning CT dataset (ie, exhale): 1 at the carina (1 slice below bifurcation) to correspond to the dose to subcarinal nodal station and another at the ipsilateral hilum (for right-sided tumors, the POI was placed just lateral to the bifurcation of the right upper lobe bronchus and bronchus intermedius; for left-sided tumors, the POI was placed just lateral to the bifurcation of the left upper lobe bronchus and the left lower lobe bronchus) to reflect the dose received by nodal stations within the hilum. Doses to each POI were obtained and converted to their normalized total dose (biologically effective dose of 2-Gy equivalent using linear quadratic equation with an α/β ratio of 10 Gy) (16).

Our lung SBRT technique has been described previously (2,17-20). All patients treated with lung SBRT at our institution were staged and worked up using a standardized protocol. Patients were eligible if they had localized NSCLC and either were deemed medically inoperable or had declined surgery. All potentially operable patients were formally assessed by a thoracic surgeon and treated with SBRT only if they declined surgery after this process. Tissue diagnosis was strongly encouraged but not mandatory. Most patients were staged with PET/CT with or without mediastinoscopy and/or endobronchial ultrasonography (EBUS fine needle aspirate).

Patients plans and treatment were developed according to our previously published institutional risk-adapted protocol (21). For peripheral tumors, earlier patients in this cohort were treated according to Radiation Therapy Oncology Group (RTOG) protocol 0236, with 60 Gy in 3 fractions (without heterogeneity correction) (1). Subsequent to the completion of the trial, patients with peripheral tumors were treated with either 48 Gy in 4 fractions for smaller tumors (<3 cm) or 54 Gy in 3 fractions for larger tumors (with heterogeneity correction). Selected cases were treated with a single fraction. Patients with central tumors were considered for the RTOG 0813 trial if eligible. Off study, these patients were treated with 50 Gy in 10 fractions or 60 Gy in 8 fractions.

We routinely performed a 4-dimensional CT (4DCT) as part of treatment planning and contoured the GTV on exhalation, inhalation, maximum intensity projection, and average CT datasets. The clinical target volume (CTV) expansion was 0 mm (ie, CTV = GTV + 0 mm). The fused CTVs formed the internal target volume (ITV). PTV was defined as the ITV+5 mm isotropic margin. Planning objectives were achieved through either a multiple beam arrangement (typically 7 co-planar and 2 non-co-planar beams) or volumetric modulated arc therapy (a full arc plus a non-co-planar partial arc) using Pinnacle. For the 3- or 4-fraction schedule, each fraction was given at least 40 hours apart. For the 8- or 10-fraction schedule, treatments were delivered daily.

Statistical analysis

All statistical analyses were conducted with SAS version 9.1 software (SAS Institute Inc., Cary, NC) for Windows (Microsoft Inc., Bellevue, WA). Categorical variables were expressed as counts and percentages. All continuous variables were expressed as means ± standard deviations. This study was designed as matched case-control design. Univariate conditional logistic regression methods were used to identify differences between the matched populations on variables of interest. The statistical significance level was chosen at a P value of .05 or less.

Results

Baseline patient and treatment characteristics are shown in Tables 1 and 2. Controls were matched to cases based on GTV and tumor location (ie, lobe). Approximately half (52.6%) of the cases had tumors located in the right upper lobe. The mean GTV and GTD values for the control group were larger than those for the cases ($P=.02$).

Overall, the baseline characteristics and prognostic factors were comparable between the cases and controls. There were more females in the control group (57.9% vs 42.1%, respectively), and overall, the controls were a slightly older population (mean age of 75 vs 72 years old, respectively). The majority of patients were staged by PET (100% of cases and 82.2% of controls), 3 patients underwent EBUS (2 cases, 1 control), and 5 patients had mediastinoscopy (1 case, 4 controls). The mean maximum standard uptake values (SUV_{max}) were similar between the 2 groups (cases 8.7 and controls 9.7). Distribution of tumor histology was also similar between the 2 groups.

With regard to treatment factors, a similar proportion of patients in each group was treated with 60 Gy in 3 fractions or 54 Gy in 3 fractions (42.1% of cases vs 44.7% of controls). There were fewer patients in the control group treated with 48 Gy in 4 fractions (36.8% of cases vs 15.8% of controls). This may be partly explained by the fact that the control group had bigger tumors. More patients in the control group were treated with 50 Gy in 10 fractions or 60 Gy in 8 fractions (21.1% of cases vs 34.2% of controls), suggesting that there were more centrally located tumors in the control group. Two patients in the control group had single-fraction treatment.

Follow-up length for the 2 groups were, again, very similar, with the control group having slightly longer follow-up (mean 2.2 years in the cases and 2.4 years in the controls). Median follow-up for the cases was 1.8 years and 1.9 years for the controls. At the time of analysis, 31.6% of cases and 55.3% of controls were still alive. Median time to relapse was 1.2 years.

With respect to the cases, a majority of them had ipsilateral hilar relapse (n=12), and all except 1 had mediastinal relapse (n=18) (Table 3). Most common sites of nodal relapse included ipsilateral hilar (n=12), ipsilateral lower paratracheal (n=8), and subcarinal (n=7). There were 2 patients with contralateral hilar relapse. Nodal recurrences were confirmed by biopsy (n=5) analysis, imaging (n=14), and PET (n=4).

On univariate logistic regression, there was a significant difference in dose to the ipsilateral hilum. Mean hilar dose for cases and controls were 9.6 Gy and 22.4 Gy, respectively ($P=.014$). When we divided the 19 nodal relapses into ipsilateral versus nonipsilateral hilar relapse, the mean

Table 2 Treatment outcomes

Variable	Mean ± SD cases of nodal relapse (%)	Mean ± SD cases without nodal relapse (%)	P value
Total dose (Gy)/fraction(s)			*
24/1	0	1 (2.6)	
34/1	0	1 (2.6)	
48/4	7 (36.8)	6 (15.8)	
50/10	1 (5.3)	6 (15.8)	
54/3	6 (31.6)	11 (28.9)	
60/3	2 (10.5)	6 (15.8)	
60/8	3 (15.8)	7 (18.4)	
SUV_{max}	8.7 ± 6.1	9.7 ± 4.7	.46
NTD to carina (Gy)	7.0 ± 7.5	9.2 ± 8.1	.13
NTD to ipsilateral hilum (Gy)	9.6 ± 12.9	22.4 ± 17.7	.014
Local relapse			
Yes	2 (10.5)	1 (2.6)	
No	17 (89.5)	37 (97.4)	
Distant relapse			
Yes	6 (31.6)	6 (15.8)	
No	13 (68.4)	32 (84.2)	
Status			
Alive NED	0	21 (55.3)	
Alive with disease	6 (31.6)	0	
Dead from Disease	13 (68.4)	5 (13.2)	
Dead NED	0	12 (31.6)	
Years to follow-up	2.15 ± 1.2	2.4 ± 1.5	

Abbreviations: NED = no evidence of disease; NTD = normalized total dose; SUV_{max} = maximum standardized uptake value.

* Where P values are not provided, statistical testing was not done because of small numbers in different categories of the variable.

Table 3 Outcomes in patients with nodal relapse

Data for cases (n=19)	No. of patients (%)	Mean ± SD normalized total dose to ipsilateral hilum (Gy)	P value
Ipsilateral hilar relapse			
No	7 (36.8)	19.8 ± 16.8	.01
Yes	12 (63.1)	3.6 ± 3.2	
Mediastinal lymph node relapse			
No	1 (5.3)		
Yes	18 (94.7)		
Years to relapse	1.23 ± 0.69		

hilar doses were 3.6 Gy (n = 12) and 19.9 Gy (n = 7), respectively ($P = .01$) (Table 3). No statistically significant differences in dose to the carina between the 2 groups were found (mean carinal dose for cases was 7.0 Gy and 9.2 Gy for controls; $P = .13$). A conditional density plot of ipsilateral hilar relapses as a function of hilar dose is shown in Figure 1, demonstrating a sigmoidal dose-effect curve.

Discussion

To our knowledge this is the first study designed to investigate the relationship between hilar dose and nodal relapse in NSCLC patients treated with lung SBRT. Because nodal recurrences were infrequent, a case-control design was believed to be the most efficient way to test the hypothesis. Such designs are subject to bias and have their limitations. Differences in relapse rates could be due to some other difference between cases and controls, rather than mere differences in incidental dose, which the matching did not properly address. Both the cases and the controls were selected from the same cohort to minimize selection bias. The same inclusion criteria were applied to both the cases and the controls. Careful attention was also paid to selecting controls with adequate follow-up to minimize survivorship bias. The data were obtained from a prospectively collected cohort. These patients were followed stringently, using a standardized protocol, and therefore, imaging frequency was comparable between the 2 groups. Nodal recurrence was determined in a consistent fashion, thus avoiding a measurement bias. We collected data for factors that may have an impact on rates of nodal recurrence, including GTD, GTV, location, adequacy of nodal staging, SUV_{max} on PET, histology subtypes, and RT dose fractionation. The nonmatched factors were comparable between the 2 groups on analysis. The investigators were blinded to the dosimetric data at the time of matching, thus eliminating a selection bias.

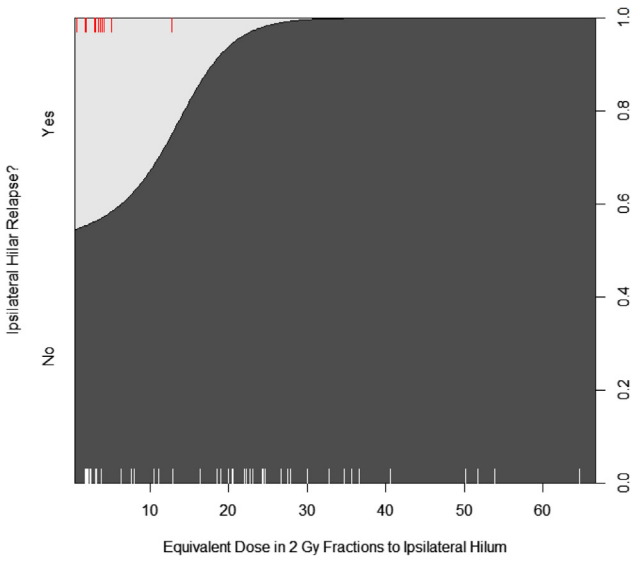

Fig. 1. Conditional density plot of ipsilateral hilar relapses as function of normalized total dose to the hilum.

Matches were based on tumor volume and tumor lobe location as these were believed to be the predominant determinants in nodal failure (12-14, 22). After matching for location, only control GTVs that were equal or greater than the case GTVs were matched. We deliberately biased the (no-nodal-relapse) control cohort with equal or larger tumors to minimize large tumor volume as a potential confounder in the (nodal relapse) case cohort as larger tumors would be expected to have higher rates of nodal relapse.

For similar reasons, we did not match for peripheral versus central tumor location. Central tumors bias the outcomes toward nodal failure but also have the highest incidental nodal doses. Therefore, the fact that incidental nodal dose appears to significantly reduce nodal failures in exactly those patients with the most central tumors appears to lend strength to our hypothesis.

Other prognostic factors such as tumor grade were not analyzed, and this may have potentially biased the results. However, SUV_{max} values on PET were comparable between the 2 groups (23), suggesting no imbalance between the groups with respect to metabolic aggressiveness. Another limitation is that cytologic confirmation of nodal status was performed only in some of the patients and that many of the patients with nodal relapse did not have cytologic confirmation or PET. Data for the location of tumor and distance from the drainage lymph nodes were not collected, as this potentially might have had an impact on the rate of nodal recurrence. We can infer this information by the dose fractionation used. More patients in the (no-nodal-relapse) controls were treated with a less biologically potent radiation regimen (either 50 Gy in 10 fractions or 60 Gy in 8 fractions) to reduce the risk of mediastinal toxicity for centrally located tumors. One would expect more centrally located tumors to have a higher rate of nodal relapse, all else held equal (13). Therefore, although we did not control for lateral proximity of tumors (peripheral vs central), we believe our findings are relevant despite these limitations.

We found there was a strong inverse correlation between the dose to the ipsilateral hilum and rates of nodal failure. A higher dose to the ipsilateral hilum was associated with fewer nodal failures. When we compared cases with ipsilateral hilum failures with those who had no failures, this relationship held true, with a higher dose to the hilum associated with lack of hilar relapse. No statistically significant associations between the dose to the subcarina and the rate of nodal failure were found (although a trend was suggested). However, the carinal dose was usually lower and, thus, less potent. Other possible causes for this include small sample size (reducing study power) and lower expected event rates for N2 versus N1 relapses.

There are several plausible reasons why nodal failure rates in SBRT literature appear to be lower than those reported in surgical series. Some investigators have suggested

that radiation therapy, particularly when given in large doses per fraction, can exert an antitumor effect outside the treatment field. This is presumably due to abscopal effect and radiation-induced immune modulation (24). In the clinical case reported, SBRT was given concurrently with a systemic agent which modulates the immune system (25). It is currently unclear whether SBRT alone would exert the same effect. The other possible explanation is that surgical series may have more patients with large centrally located tumors and hence a higher probability of nodal relapse. The counterargument for this is that patients who had surgery would have had lymph node dissection and adjuvant chemotherapy when appropriate, so in fact, one may expect patients in surgical series to show lower rates of nodal relapse than patients treated with SBRT alone. It is always difficult to compare outcomes for different treatment modalities as the patient population is different. We hypothesize that the difference in nodal relapse rate was due to unintentional incidental dose to the ipsilateral hilum. Biologically this makes sense as cancer often metastasizes in a predictable fashion. In the case of lung malignancy, the ipsilateral hilum represents the first-echelon node. Despite the very conformal dosimetry achieved by typical SBRT plans, we have demonstrated that the ipsilateral hilum and subcarinal region still receives a small but significant dose as a result of low-dose splash. Similarly, in their series of 38 patients treated with lung SBRT to a dose of 60 Gy in 3 fractions, Martin et al (26) found that the mean incidental doses to the ipsilateral hilar nodes were between 15.6 and 21.5 Gy for lower lobe tumors. Our results and those of Martin et al (26) support this hypothesis and raise the need for further validation and investigation.

The notion of prophylactic nodal irradiation is not a new one (27, 28). However, the threshold dose required to eliminate microscopic disease is less clear. Withers et al (29) reported that 50 Gy in 2-Gy fractions can achieve an overall 90% reduction in the incidence of metastases. In the setting of NSCLC, Kepka et al (30) concluded that doses lower than 50 Gy can effectively eradicate subclinical metastatic deposits. In one sense, the need for prophylactic nodal irradiation depends on the absolute risk of nodal relapse and also what is deemed an "acceptable" nodal relapse rate, where no further intervention is required. In the setting of NSCLC treated with conventional radiation therapy, many have argued that elective nodal irradiation is not necessary, as isolated nodal failure rates are less than 10% in many retrospective single-institution series (31, 32). This argument makes sense because the rates of local and distant failure are high in this population. In contrast, patients treated with SBRT obtain excellent local control with low rates of distant relapse; nodal relapse rates are on the order of 10% (2, 9). Therefore, the idea of being able to identify a subset of patients who are at higher risk of nodal relapse and offer prophylactic nodal radiation therapy in this setting is attractive.

There appears to be a dose threshold effect at approximately 20 Gy (Fig. 1). The apparent doses needed for prophylactic treatment against nodal relapses are radiobiologically less potent than typical adjuvant doses used to sterilize microscopic disease (such as 45 Gy in 25 fractions). The next research goal is to identify a high-risk subset that might benefit from prophylactic nodal irradiation. Because of the case-matched design, we cannot make any generalizations about the entire SBRT populations such as the impact of tumor size on nodal relapses, but this will be the subject for future study. Toxicity outcomes of patients who received a higher incidental nodal dose versus low incidental nodal dose also warrant further investigation.

Conclusions

In conclusion, incidental hilar doses greater than 20 Gy are associated with fewer nodal relapses in inoperable early stage NSCLC patients treated with SBRT.

References

1. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010;303:1070-1076.
2. Taremi M, Hope A, Dahele M, et al. Stereotactic body radiotherapy for medically inoperable lung cancer: prospective, single-center study of 108 consecutive patients. *Int J Radiat Oncol Biol Phys* 2012;82:967-973.
3. Baumann P, Nyman J, Hoyer M, 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;27:3290-3296.
4. Martin A, Gaya A. Stereotactic body radiotherapy: A review. *Clin Oncol (R Coll Radiol)* 2010;22:157-172.
5. Nagata Y, Matsuo Y, Takayama K, et al. Current status of stereotactic body radiotherapy for lung cancer. *Int J Clin Oncol* 2007;12:3-7.
6. Palma D, Visser O, Lagerwaard FJ, et al. Treatment of stage I NSCLC in elderly patients: A population-based matched-pair comparison of stereotactic radiotherapy versus surgery. *Radiother Oncol* 2011;101:240-244.
7. Palma D, Visser O, Lagerwaard FJ, et al. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: A population-based time-trend analysis. *J Clin Oncol* 2010;28:5153-5159.
8. Rowell NP, Williams CJ. Radical radiotherapy for stage I/II non-small cell lung cancer in patients not sufficiently fit for or declining surgery (medically inoperable): A systematic review. *Thorax* 2001;56:628-638.
9. Chi A, Liao Z, Nguyen NP, et al. Systemic review of the patterns of failure following stereotactic body radiation therapy in early-stage non-small-cell lung cancer: Clinical implications. *Radiother Oncol* 2010;94:1-11.
10. Timmerman RD. Surgery versus stereotactic body radiation therapy for early-stage lung cancer: Who's down for the count? *J Clin Oncol* 2010;28:907-909.
11. Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. *J Clin Oncol* 2010;28:928-935.
12. Fuwa N, Mitsudomi T, Daimon T, et al. Factors involved in lymph node metastasis in clinical stage I non-small cell lung cancer—from studies of 604 surgical cases. *Lung Cancer* 2007;57:311-316.
13. Cho S, Song IH, Yang HC, et al. Predictive factors for node metastasis in patients with clinical stage I non-small cell lung cancer. *Ann Thorac Surg* 2013;96:239-245.

14. Saynak M, Veeramachaneni NK, Hubbs JL, et al. Local failure after complete resection of N0-1 non-small cell lung cancer. *Lung Cancer* 2011;71:156-165.
15. Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. *Chest* 1997;111:1718-1723.
16. Flickinger JC, Kalend A. Use of normalized total dose to represent the biological effect of fractionated radiotherapy. *Radiother Oncol* 1990; 17:339-347.
17. Dahele M, Pearson S, Purdie T, et al. Practical considerations arising from the implementation of lung stereotactic body radiation therapy (SBRT) at a comprehensive cancer center. *J Thorac Oncol* 2008;3: 1332-1341.
18. Purdie TG, Bissonnette JP, Franks K, et al. Cone-beam computed tomography for on-line image guidance of lung stereotactic radiotherapy: Localization, verification, and intrafraction tumor position. *Int J Radiat Oncol Biol Phys* 2007;68:243-252.
19. Purdie TG, Moseley DJ, Bissonnette JP, et al. Respiration correlated cone-beam computed tomography and 4DCT for evaluating target motion in stereotactic lung radiation therapy. *Acta Oncol* 2006;45:915-922.
20. Bissonnette JP, Franks KN, Purdie TG, et al. Quantifying interfraction and intrafraction tumor motion in lung stereotactic body radiotherapy using respiration-correlated cone beam computed tomography. *Int J Radiat Oncol Biol Phys* 2009;75:688-695.
21. Dahele M, Brade A, Pearson S, et al. Stereotactic radiation therapy for inoperable, early-stage non-small-cell lung cancer. *CMAJ* 2009;180: 1326-1328.
22. Giraud P, De Rycke Y, Lavole A, et al. Probability of mediastinal involvement in non-small-cell lung cancer: A statistical definition of the clinical target volume for 3-dimensional conformal radiotherapy? *Int J Radiat Oncol Biol Phys* 2006;64:127-135.
23. Al-Sarraf N, Gately K, Lucey J, et al. Clinical implication and prognostic significance of standardised uptake value of primary non-small cell lung cancer on positron emission tomography: Analysis of 176 cases. *Eur J Cardiothorac Surg* 2008;34:892-897.
24. Finkelstein SE, Timmerman R, McBride WH, et al. The confluence of stereotactic ablative radiotherapy and tumour immunology. *Clin Dev Immunol* 2011;2011:439752.
25. Postow MA, Callahan MK, Barker CA, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. *N Engl J Med* 2012; 366:925-931.
26. Martin KL, Gomez J, Nazareth DP, et al. Quantification of incidental mediastinal and hilar irradiation delivered during definitive stereotactic body radiation therapy for peripheral non-small cell lung cancer. *Med Dosim* 2012;37:182-185.
27. Jeremic B. Incidental irradiation of nodal regions at risk during limited-field radiotherapy (RT) in dose-escalation studies in nonsmall cell lung cancer (NSCLC). Enough to convert no-elective into elective nodal irradiation (ENI)? *Radiother Oncol* 2004;71:123-125.
28. Rosenman JG, Xie L, Marks LB. Selective elective nodal irradiation: "Let's head 'em off at the pass" *Int J Radiat Oncol Biol Phys* 2011;81: 1208-1210.
29. Withers HR, Peters LJ, Taylor JM. Dose-response relationship for radiation therapy of subclinical disease. *Int J Radiat Oncol Biol Phys* 1995;31:353-359.
30. Kepka L, Maciejewski B, Withers RH. Does incidental irradiation with doses below 50 gy effectively reduce isolated nodal failures in non-small-cell lung cancer: Dose-response relationship. *Int J Radiat Oncol Biol Phys* 2009;73:1391-1396.
31. Rosenzweig KE, Sim SE, Mychalczak B, et al. Elective nodal irradiation in the treatment of non-small-cell lung cancer with three-dimensional conformal radiation therapy. *Int J Radiat Oncol Biol Phys* 2001;50:681-685.
32. Sulman EP, Komaki R, Klopp AH, et al. Exclusion of elective nodal irradiation is associated with minimal elective nodal failure in non-small cell lung cancer. *Radiat Oncol* 2009;4:5.