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Brachial Plexopathy in Apical Non-Small Cell Lung Cancer Treated With Definitive Radiation: Dosimetric Analysis and Clinical Implications

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Summary

Radiation-induced brachial plexopathy (RIBP) and tumor-related brachial plexopathy (TRBP) were retrospectively studied in apical NSCLC patients treated with definitive radiation therapy. Our results demonstrate that RIBP is a relatively uncommon complication, despite delivering doses that exceed historical dose constraints. TRBP is associated with significant debilitating morbidity and commonly occurs in patients who develop primary tumor failures. Our study suggests that the clinical importance

Purpose: Data are limited on the clinical significance of brachial plexopathy in patients with apical non-small cell lung cancers (NSCLC) treated with definitive radiation therapy. We report the rates of radiation-induced brachial plexopathy (RIBP) and tumor-related brachial plexopathy (TRBP) and associated dosimetric parameters in apical NSCLC patients.

Methods and Materials: Charts of NSCLC patients with primary upper lobe or superiorly located nodal disease who received $\geq$50 Gy of definitive conventionally fractionated radiation or chemoradiation were retrospectively reviewed for evidence of brachial plexopathy and categorized as RIBP, TRBP, or trauma-related. Dosimetric data were gathered on ipsilateral brachial plexuses (IBP) contoured according to Radiation Therapy Oncology Group atlas guidelines.

Results: Eighty patients were identified with a median follow-up and survival time of 17.2 and 17.7 months, respectively. The median prescribed dose was 66.6 Gy (range, 50.4-84.0), and 71% of patients received concurrent chemotherapy. RIBP occurred in 5 patients with an estimated 3-year rate of 12% when accounting for competing risk of death. Seven patients developed TRBP (estimated 3-year rate of 13%), comprising 24% of patients who developed locoregional failures. Grade 3 brachial plexopathy was more common in patients who experienced TRBP than RIBP (57% vs 20%). No patient who received $\leq$78 Gy to the IBP developed RIBP. On multivariable competing risk analysis, IBP V76 receiving $\geq$1 cc, and primary tumor failure had the highest hazard ratios for developing RIBP and TRBP, respectively.

Conclusions: RIBP is a relatively uncommon complication in patients with apical NSCLC tumors receiving definitive doses of radiation, while patients who develop primary tumor failures are at high risk for developing morbid TRBP. These findings suggest that the importance

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of controlling primary disease outweighs the relatively low risk of RIBP in this patient population.

of primary tumor control with adequate doses of radiation outweigh the risk of RIBP in this population of patients.

Introduction

The prognosis of locally advanced non-small cell lung cancer (NSCLC) is poor, with 5-year overall survival rates of 15%-25% (1). In addition to systemic failures, there is also a high risk of local failures, with rates of 50% or more in most modern studies, highlighting the fact that this is a significant problem as well in these patients (1). Tumors located in the apex of the lung pose unique local treatment challenges due to their close proximity to the spine, critical peripheral nerves, and major vasculature. For patients treated with definitive radiation therapy, the radiation treatment fields often include the ipsilateral brachial plexus, a network of nerve fibers that innervate the arm and hand.

Historical dose constraints of the brachial plexus have been in the range of 60-66 Gy (2). Radiation-induced brachial plexopathy (RIBP) manifests as upper extremity paresthesias, motor weakness, and neuropathic pain (3). In the setting of radiation dose escalation for NSCLC, which has been demonstrated in multiple phase II studies to be safe and feasible with concurrent chemotherapy to doses up to 74 Gy (1, 4), there is risk for potentially exceeding this radiation dose tolerance in apically located tumors.

Data for RIBP in NSCLC patients treated with curative intent are limited. The clinical significance of exceeding the historical dose constraints for the brachial plexus is not known in this group of patients. Furthermore, the risk of brachial plexopathy from local tumor progression or tumor-related brachial plexopathy (TRBP) must be balanced against the risk of RIBP. In this study, we sought to assess the rate and characteristics of RIBP and TRBP, as well as analyze the clinical and dosimetric factors associated with these complications in patients with apical NSCLC.

Methods and Materials

Patient population

We retrospectively reviewed the charts of NSCLC patients treated with conventionally fractionated radiation therapy with curative intent at the University of Pennsylvania from 2003-2010, after approval from the institutional review board. Patients with primary upper lobe tumors or nodal disease located in the superior mediastinum or supraclavicular fossa were identified. Of these patients, we identified patients who received $\geq$50 Gy to the primary tumor and supraclavicular fossa, which was used as a dosimetric surrogate for the brachial plexus prior to contouring of the brachial plexus. Demographic, treatment, outcomes, and dosimetric data were collected from these patient charts. All outcome data were calculated from the end of radiation treatment to time of event.

Evaluation of brachial plexopathy

All available medical records of these patients were reviewed for clinical and radiographic evidence of brachial plexopathy. Brachial plexopathy was a clinical diagnosis defined as regional paresthesias of the brachial plexus, marked discomfort and muscle weakness, and/or limited movement in the arm or hand following completion of radiation therapy and was graded, according to Common Terminology Criteria for Adverse Events version 4 (CTCAE v4.03), as grade 1, asymptomatic, clinical or diagnostic observations only, intervention not indicated; grade 2, moderate symptoms, limiting instrumental activities of daily living; or grade 3, severe symptoms, limiting self-care activities of daily living.

Patients were not considered to have brachial plexopathy if they had signs of polyneuropathy or if neurological symptoms were attributable to bony or brain metastases. Patients who had symptoms of brachial plexopathy prior to definitive treatment were noted but not included in the analysis unless the severity or nature of their symptoms changed after treatment.

The etiology of brachial plexus symptoms was divided into 3 groups: RIBP, TRBP, or trauma-related neuropathy. RIBP was defined as symptomatic brachial plexopathy occurring after completion of radiation therapy and without evidence of local tumor involvement or trauma. TRBP was identified as symptomatic brachial plexopathy with documented radiographic evidence of local tumor progression that was in close proximity or adjacent to the brachial plexus. Trauma-related neuropathy was defined as neurological symptoms attributable to orthopedic interventions or known osteoarthropathy. Time to brachial plexopathy was defined from the end of radiation treatment to the clinical diagnosis of brachial plexopathy.

Dosimetric analysis

Ipsilateral brachial plexus (IBP) was retrospectively delineated according to published Radiation Therapy Oncology Group atlas guidelines (5), which has been validated as being reproducible in head and neck treatment planning (6) and reviewed for accuracy and consistency by one investigator (S.A.). The following dosimetric parameters were collected: IBP dose, gross tumor volume (GTV) size, and tumor distance from the lung apex (perpendicular distance between the most superior aspect of the primary tumor and the most apical aspect of the first rib). For patients in whom the IBP could not be contoured secondary to motion or metallic or tumor artifact, other dosimetric (GTV size, tumor to lung apex distance) and clinical information were still gathered.

Statistical analysis

The Kaplan-Meier method was used to estimate locoregional control, disease-free survival, and overall survival (OS) rates. Because a patient could have died before experiencing RIBP or TRBP, which alters the probability of experiencing the event of interest, we used a competing risks approach in these analyses. We computed the cumulative probability of RIBP accounting for the competing risk of death, using nonparametric cumulative incidence functions. We also used the Fine-Gray semiparametric

model for subdistribution hazards to estimate the effects of covariates in multivariable models.

Univariate competing risk regression analysis was used to identify individual factors associated with the development of RIBP and TRBP. Any factor with a P value of $\leq .20$ on univariate analysis was eligible for subsequent multivariable regression analysis. A threshold P value of $\leq .05$ was used to determine significance on multivariable modeling. Descriptive statistics were performed using STATA version 11 software (StataCorp, College Station, TX). Competing risks analysis was performed using R version 2.14 software (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

A total of 142 patients were identified as having primary upper lobe tumors or nodal disease located in the superior mediastinum or supraclavicular fossa. Of these patients, 80 patients received $\geq$50 Gy to the primary tumor and supraclavicular fossa (Table 1). The majority had locally advanced disease (78%) and nearly all (90%) patients received chemotherapy, most commonly with a concurrent regimen (71%). The most common chemotherapy regimens used were cisplatin and etoposide (n = 31) or carboplatin and paclitaxel (n = 14). The median follow-up time and survival time was 17.2 months and 17.7 months, respectively. The median follow-up time for survivors was 30.8 months.

Brachial plexopathy

Clinical symptoms consistent with brachial plexopathy were identified in 17 of 80 patients (21%). Six of these patients had symptoms attributed to trauma or osteoarthropathy, and 11 patients (14%) had evidence of RIBP or TRBP. Among the 11 patients, 5 patients were found to have RIBP (Supplementary Fig. E1). Of the 56 patients who were estimated to have received $\geq$60 Gy to the IBP, the crude rate of RIBP was 9%. The estimated rates of RIBP at 1 and 3 years were 8% and 17%, respectively. However, when we accounted for the competing risk of death, the competing risk adjusted rates of RIBP decreased to 6% and 12%, respectively (Fig. 1).

Seven patients were identified has having TRBP (Supplementary Fig. E2), comprising 24% of the patients who developed locoregional failures (n = 29). Of the 59 patients with tumors located within 3 cm of the lung apex, the crude rate of TRBP was 12%. The estimated rate of TRBP at 3 years was 13%. One patient developed both TRBP and RIBP at different

Table 1 Clinical patient characteristics

Characteristic	Total no. (%)	RIBP (%)	TRBP (%)
No. of patients	80	5	7
Age (y)			
Mean (±SEM)	62.6 ± 1.3	66.0 ± 4.4	53.6 ± 2.7
Median (range)	61 (35-95)	73 (53-73)	53 (46-66)
Gender			
Male	31 (39%)	1 (20%)	2 (29%)
Female	49 (61%)	4 (80%)	5 (71%)
Stage			
I	5 (6%)	0 (0%)	0 (0%)
II	5 (6%)	2 (40%)	1 (14%)
III	62 (78%)	3 (60%)	6 (86%)
IV	8 (10%)	0 (0%)	0 (0%)
Tumor Location			
Right upper lobe	48 (60%)	3 (60%)	5 (71%)
Left upper lobe	23 (29%)	2 (40%)	2 (29%)
Supraclavicular node	5 (7%)	0 (0%)	0 (0%)
Superior mediastinal node	4 (5%)	0 (0%)	0 (0%)
Chemotherapy			
None	8 (10%)	0 (0%)	0 (0%)
Sequential	15 (19%)	3 (60%)	4 (57%)
Concurrent	57 (71%)	2 (40%)	3 (43%)
Prescribed Total Dose (Gy)			
Mean ± SEM	68.6 ± 0.7	77.6 ± 1.6	65.9 ± 3.0
Median (range)	66.6 (50.4-84.0)	80.0 (72.0-80.0)	66.6 (50.4-76.0)
Dose per fraction (Gy)			
Mean ± SEM	1.85 ± 0.0	1.96 ± 0.0	1.83 ± 0.0
Median (range)	1.8 (1.8-2.0)	2.0 (1.8-2.0)	1.8 (1.8-2.0)
Follow-up (months)			
Mean ± SEM	20.2 ± 1.8	30.2 ± 6.8	14.1 ± 5.5
Median (range)	17.2 (0-61.0)	30.9 (9.0-45.4)	8.4 (3.8-45.4)

Abbreviations: RIBP = radiation-induced brachial plexopathy; SEM = standard error of the mean; TRBP = tumor-related brachial plexopathy.

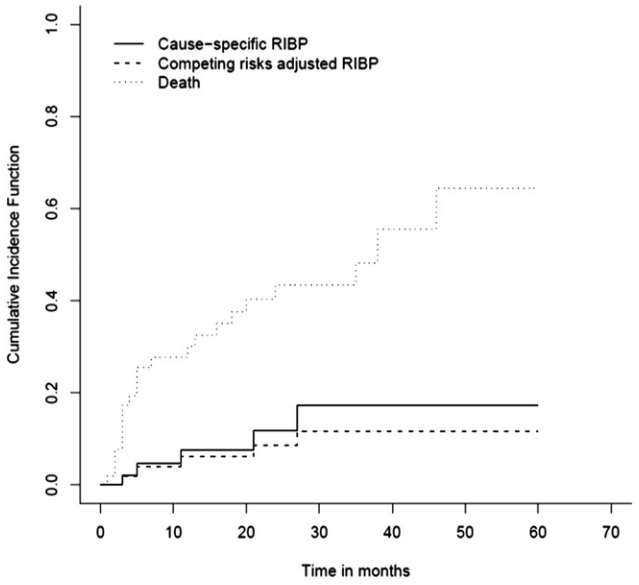

Fig. 1. Cumulative incidence curves for RIBP (with death as the censoring event), death, and competing risks adjusted for RIBP (where death is considered to be a competing risk).

time intervals (first with TRBP, then with RIBP after reirradiation for local progression) and was included in both the TRBP and RIBP analyses.

The median onset of brachial plexopathy occurred earlier in patients who developed TRBP compared to patients who developed RIBP: 4 months (range, 1-17) vs 11 months (range, 4-27), respectively. The most common neurologic symptom was neuropathic pain, which was present in all patients with brachial plexopathy. Paresthesia in the form of tingling and/or numbness in the ipsilateral upper extremity was seen in 80% (n=4) of patients with RIBP and in 43% (n=3) of patients with TRBP. Motor weakness was equally present in patients with RIBP (60%; n=3) and TRBP (57%; n=4).

The severity of symptoms was more disabling for patients who developed TRBP, with 57% (n=4) developing grade 3 brachial plexopathy compared to 20% (n=1) in patients with RIBP (Supplementary Fig. E3). Among TRBP patients, 71% (n=5) required multiple narcotics, including both short-acting and long-acting opioid agents, to control symptoms of neuropathic pain, compared with 40% (n=2) of RIBP patients. Pentoxifylline (Trental; Aventis) and vitamin E were initially used to treat the symptoms of 2 patients with RIBP but proved relatively ineffective; these patients eventually required the addition of an opioid analgesic to manage symptoms.

Brachial plexus dosimetric analysis

Dosimetric analysis was performed in 76 patients (Table 2). Four of the 80 patients had motion or tumor artifacts that prohibited contouring of the brachial plexus, including 2 who were identified as having TRBP. Primary tumor volumes were relatively large and located close to the lung apex, most commonly located within 1 cm of the apex.

The IBP maximum doses (D_{max}) were ≥60 Gy, 66 Gy, 70 Gy, 74 Gy, 76 Gy, 78 Gy, and 80 Gy in 52, 40, 25, 19, 16, 11, and 7 patients, respectively (Fig. 2). No patient who received ≤78 Gy

Table 2 Dosimetric analysis of patients with radiation-induced (RIBP) and tumor-related (TRBP) brachial plexopathy

Characteristic	RIBP (n=5)	TRBP (n=7)*
Gross tumor volume size (cc)		
Mean (±SEM)	164.8 ± 59.0	199.5 ± 82.0
Median (range)	107.3 (53.0-377.1)	163.2 (24.4-664.2)
Tumor to lung apex distance (cm)		
Mean (±SEM)	0.80 ± 0.25	0.70 ± 0.31
Median (range)	0.75 (0-1.36)	0.60 (0-2.40)
IBP volume (cc)		
Mean (±SEM)	10.4 ± 1.6	8.1 ± 0.9
Median (range)	10.3 (6.8-16.3)	8.6 (5.2-10.3)
Mean IBP dose (Gy)		
Mean (±SEM)	51.9 ± 8.5	36.4 ± 7.2
Median (range)	56.4 (31.1-71.3)	36.9 (12.6-56.4)
IBP D_{max} (Gy)		
Mean (±SEM)	83.3 ± 2.4	68.0 ± 4.8
Median (range)	81.5 (78.1-90.9)	66.3 (52.6-81.5)
Mean IBP V60		
Absolute (cc)	5.8 ± 1.8	2.5 ± 1.1
Relative (%)	54.2%	29.2%
Mean IBP V66		
Absolute (cc)	5.5 ± 1.8	1.6 ± 1.0
Relative (%)	51.0%	16.3%
Mean IBP V70		
Absolute (cc)	5.2 ± 1.9	1.4 ± 0.9
Relative (%)	48.1%	14.3%
Mean IBP V74		
Absolute (cc)	4.8 ± 1.9	0.8
Relative (%)	43.5%	7.6%
Mean IBP V76		
Absolute (cc)	4.4 ± 2.0	0.7
Relative (%)	39.2%	6.8%
Mean IBP V78		
Absolute (cc)	3.3 ± 2.2	0.5
Relative (%)	24.8%	5.2%
Mean IBP V80		
Absolute (cc)	3.0 ± 2.2	0.3
Relative (%)	21.9%	2.7%

Abbreviation: IBP = ipsilateral brachial plexus.
* IBP dosimetric analyses were performed in 5 patients due to imaging artifacts in 2 of the patients.

D_{max} to the IBP developed RIBP. Five of 11 patients who received ≥78 Gy and 3 of 7 patients who received ≥80 Gy to the IBP developed RIBP. Patients who developed RIBP had significant volumes of their IBP irradiated to doses above 66 Gy: mean V66 Gy 51%, V76 Gy 39%, V80 Gy 22% (Table 2).

Associated factors for brachial plexopathy

Univariate and multivariable competing risk analyses were performed to identify potential clinical and dosimetric factors associated with RIBP (Table 3) and TRBP (Table 4). Total prescribed radiation dose and dose to the IBP were statistically significant for the development of RIBP in univariate analysis and remained significant on multivariable analysis (only the IBP dose was included in the multivariable analysis because IBP dose and total

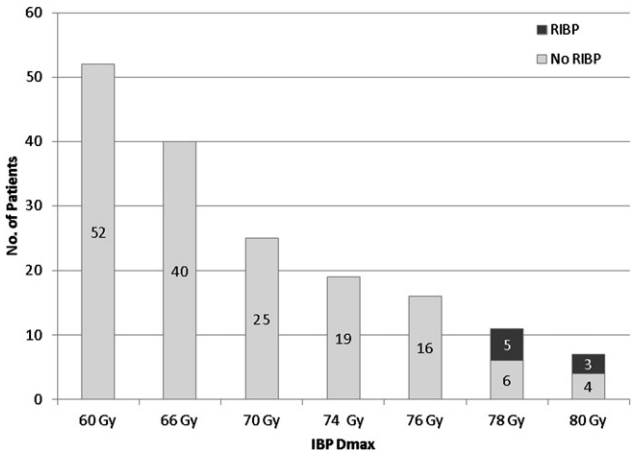

Fig. 2. Cumulative rate of RIBP as a function of maximal dose delivered to the IBP.

dose are closely related). The IBP V76 of ≥1 cc had the highest hazard ratio (HR) of 18.36 ($P = .03$). Stage, tumor size, and tumor distance to lung apex were statistically significant on univariate analysis but were not statistically significant on multivariable analysis.

For TRBP patients, age, total prescribed dose, and presence of primary tumor failure were statistically significant on univariate analysis. However, only age and primary tumor failure remained statistically significant on multivariable analysis. Patients who had evidence of primary tumor failure had an HR of 13.1 ($P = .02$) for developing TRBP.

Patient outcomes

The estimated 2-year locoregional control, disease-free survival, and OS rates were 30%, 28%, and 38%, respectively. Patients who developed RIBP had longer survival times than the patients who developed TRBP. The 2-year OS rates was 60% for patients with RIBP (median follow-up 30.9 months; range, 9.0-45.4), compared to 14% for patients with TRBP (median follow-up 8.4 months; range 3.8-45.4). In addition, patients who developed TRBP had worse survival outcomes than patients who developed locoregional failures. Among patients in the total population of 80 patients who developed locoregional failures (n = 29), the median follow-up was 17.9 months, and the 2-year OS rate was 35%.

Discussion

Apical NSCLC tumors pose a unique challenge for radiation oncologists, who must balance the need to control primary tumor disease and prevent tumor-related morbidity against the risk of exceeding the dose constraint of the brachial plexus and causing RIBP. In these patients, we found that the IBP commonly receives radiation doses in excess of 66 Gy (50% in our study), which is the brachial plexus dose constraint currently being used in ongoing Radiation Therapy Oncology Group trials for NSCLC (7). Our study demonstrates that RIBP is a relatively uncommon complication of definitive treatment for apical NSCLC tumors, while symptomatic TRBP is a significant risk if the primary tumor is not controlled.

The risk of RIBP was relatively low (estimated 3-year rate, 12%) and most commonly presented with mild to moderate symptoms. Although the rate of TRBP was also relatively low (estimated 3-year rate 13%), nearly 25% of patients who developed locoregional failures eventually suffered symptomatic brachial plexopathy from local tumor progression that was often severely debilitating (57% had grade 3).

The frequency of RIBP in our series is consistent with that in breast cancer studies, where 1%-9% of women receiving radiation with conventional fractionation to the supraclavicular and axillary fields showed symptoms of RIBP with longer follow-up than in our series (8, 9). In other studies, the development of radiation-induced morbidity was associated with concomitant use of chemotherapy, higher total radiation doses, and larger fraction sizes (9-12). In our study, it was not possible to assess the effect of concurrent chemotherapy on the development of RIBP due to the

Table 3 Radiation-induced brachial plexopathy: univariate and multivariate competing risk analyses in patients receiving ≥60 Gy to the brachial plexus ($n = 52$*)

	Univariate			Multivariable		
Variable	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (y)	1.02	0.98-1.07	.31			
Gender (M/F)	2.73	0.30-24.6	.37			
Stage (I-IV)	0.47	0.22-1.03	.06	0.59	0.32-1.10	.10
Laterality (R/L)	0.58	0.10-3.27	.54			
Tumor size (cm)	0.99	0.99-1.00	.19	1.00	1.00-1.00	.86
Tumor to lung apex distance (cm)	0.64	0.41-1.00	.05	0.46	0.21-1.00	.05
Concurrent chemotherapy (yes/no)	0.31	0.05-1.89	.21			
Dose (Gy)	1.21	1.09-1.34	<.01			
IBP Dmax (Gy)	1.27	1.16-1.39	<.01			
IBP V60 (cc)	1.41	1.06-1.88	.02			
IBP V66 (cc)	1.47	1.20-1.79	<.01			
IBP V76 (cc)	1.51	1.22-1.87	<.01			
≥1 cc	22.23	2.63-188.0	.004	18.36	1.38-244.8	.03
IBP V80 (cc)	1.43	1.25-1.65	<.01			

Abbreviations: CI = confidence interval; HR = hazard ratio; IBP = ipsilateral brachial plexus.
* Four patients were excluded due to imaging artifacts prohibiting dosimetric analysis of IBP.

Table 4 Tumor-related brachial plexopathy: univariate and multivariate competing risk analyses in patients with primary tumors located within 3 cm of the lung apex ($n=55$*)

Variable	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (y)	0.93	0.88-0.98	.01	0.91	0.85-0.97	.01
Gender (M/F)	1.15	0.22-6.14	.87			
Stage (I-IV)	0.82	0.38-1.79	.63			
Laterality (R/L)	1.58	0.19-13.3	.68			
Tumor size (cm)	1.00	1.00-1.00	.48			
Tumor to lung apex distance (cm)	0.58	0.22-1.56	.28			
Concurrent chemotherapy (yes/no)	0.86	0.16-4.68	.86			
Dose (Gy)	0.89	0.82-0.96	<.01	0.90	0.79-1.04	.15
Histology (adenocarcinoma)	2.77	0.34-22.8	.34			
Primary tumor failure	16.6	1.92-143.3	.01	13.1	1.41-120.5	.02

Abbreviations: CI = confidence interval; HR = hazard ratio.

* Four patients were excluded due to tumor or motion artifacts prohibiting dosimetric analysis of IBP.

small number of RIBP events. Furthermore, it was not possible to examine the effect of larger fraction sizes because all patients received a conventional fractionation schedule of 1.8-2.0 Gy.

We analyzed various clinical and dosimetric variables to determine which patients were at highest risk for developing RIBP and TRBP. No patient who received a maximum dose of $\leq$78 Gy to the brachial plexus developed RIBP. However, the irradiated volume of the brachial plexus also appeared to be associated with RIBP. A significant portion of the brachial plexus received high doses of radiation that exceed the historical dose constraint of 60-66 Gy in our series (Table 2). It is unclear whether the brachial plexus D_{max} or partial volumes receiving high doses of radiation were more important in RIBP. In our multivariable analysis, delivering $\geq$76 Gy to more than 1 cc of the brachial plexus was found to have the highest risk for developing RIBP (HR, 18) among all dosimetric variables analyzed.

Taken together, these data suggest that in addition to the maximum dose that the brachial plexus receives, the volume of irradiated brachial plexus also appears to play a role in RIBP. Our findings are in accordance with those of other studies that showed an association between radiation dose and the development of RIBP (2). It is important to note that the intent to analyze dosimetric data in our study was not to define the absolute brachial plexus tolerance to radiation, which would require a much larger set of patients and longer follow-up time, but rather to provide data to guide clinical decisions when weighing the risks of RIBP and TRBP.

In regard to TRBP, the presence of primary tumor failure was significantly correlated with the risk of TRBP (odds ratio, 13). Interestingly, the size of the primary tumor was not correlated with the development of TRBP. Previous studies have demonstrated that increasing tumor size is correlated with risk of local failure (13, 14). It could be postulated that a bulky primary tumor would also have an increased risk for TRBP. However, a large primary tumor that is located relatively distant from the lung apex is unlikely to encroach upon the brachial plexus and cause symptoms.

We recognize that the frequency of brachial plexopathy may be underreported in our study due to various limitations. Because of the retrospective nature of our study, patients were not prospectively examined for signs and symptoms of neurotoxicity by clinicians or neurologists. Patients with subtle or undocumented signs or symptoms of brachial plexopathy may have been missed. In addition, patients that may have had abnormal findings on electrophysiological tests such as electromyogram, which is indicative of RIBP, in the absence of neurologic symptoms (grade 1 brachial plexopathy) were likely to have not been captured.

Second, it is possible that patients with TRBP also had symptoms of plexopathy attributable to radiation injury and vice versa, as demonstrated by 1 patient in our series who was documented as having both TRBP and RIBP at different times. Despite the availability of magnetic resonance imaging (15) and positron emission tomography (16) as useful diagnostic tools to identify neoplastic involvement of the brachial plexus and recurrent tumor masses, there exists overlap between the imaging findings of RIBP and TRBP. Therefore, no reliable noninvasive diagnostic modality currently exists to reliably detect the occurrence of both forms of brachial plexopathy concurrently. Conservatively, the combined crude rate of RIBP and TRBP in our series was 15%.

Last, with a relatively short median follow-up time of only 17 months for all 80 patients, the entire spectrum of radiation toxicity to the brachial plexus is not likely to be captured. In other series, neurologic symptoms have occurred during a latency interval ranging from a few months to more than 30 years after treatment, in some cases (3, 8, 11). The peak onset of plexus neuropathies typically develops within 1-4 years following radiation therapy (12) compared to a median onset of 11 months from the completion of radiation in our study. Continued follow-up exceeding 5-10 years will be important in establishing the long-term rate of RIBP. However, this particular limitation may not be as relevant in a patient population that may not survive long enough (2-year OS rate of only 40%) to develop late RIBP.

Conclusions

Our study demonstrates that while both RIBP and TRBP are both relatively uncommon events in the definitive treatment for apical NSCLC tumors, TRBP is frequently morbid and is a significant risk if the primary tumor is not controlled. In this population of patients in whom long-term survival is often limited, patients may not survive long enough to develop long-term morbidity from radiation-mediated brachial plexus injury. On balance, the clinical importance of controlling primary disease outweighs the risk of

radiation-induced morbidity when exceeding historic dose constraints. We recommend treating locally advanced nonoperable primary apical tumors located in close proximity to the brachial plexus (<1-2 cm from the lung apex or brachial plexus) with concurrent chemoradiation to doses of 66-74 Gy, while limiting the hot spots in the brachial plexus to a D_{max} of $\leq$78 Gy and V76 of $\leq$1 cc to minimize the risk of RIBP. These recommendations will continue to be further refined as additional data and longer follow-up times are obtained.

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