Effect of Tumor Size on Prognosis in Patients Treated with Radical Radiotherapy or Chemoradiotherapy for Non–Small Cell Lung Cancer

An Analysis of the Staging Project Database of the International Association for the Study of Lung Cancer

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Background: Analysis of the International Association for the Study of Lung Cancer database revealed that for patients with completely resected, node-negative, non–small-cell lung cancer (NSCLC), increasing tumor size was associated with worsening survival. This analysis was performed to determine the effect of size on prognosis in patients in the same database but who were treated with radiotherapy or chemoradiotherapy.

Methods: Patients were eligible if they had pathologically confirmed NSCLC, no evidence of distant metastases, intended treatment was radical radiotherapy (minimum 50 Gy) or combined chemotherapy and radiotherapy, no surgery, and tumor diameter was available.

Results: Eight hundred and sixty-eight patients were available for analysis. Patient characteristics were: sex (men) 65.3%; median age 64 years (range, 32–88); Eastern Cooperative Oncology Group performance status 0: 55%, 1: 33%, 2 or more: 5%; chemotherapy 74%; no chemotherapy 18%; weight loss less than 5 %: 70%, and more than 5%: 25%. Primary tumor size was categorized according to tumor, node, metastasis 7th edition. On univariate analysis, the following factors were prognostic for survival: age (continuous) (p = 0.0035); performance status of 1 or more (p = 0.0021); weight loss less than 5% ($p < 0.0001$); chemotherapy (p = 0.0189); and primary tumor size (continuous) (p = 0.0002). Sex and clinical nodal stage were not significant. On multivariate analysis, age and weight loss remained significant factors for survival, as was tumor size less than 3 cm.

Conclusions: In patients treated with radiotherapy with or without chemotherapy, tumor size less than 3 cm was associated with longer survival than larger tumors. Evidence of the effect of size on prognosis above this was weak. Five-year survival of more than 10% was observed in all four size categories.

Key Words: Non–small-cell lung cancer, Radiotherapy, Prognosis, Tumor, node, metastasis stage, Tumor size.

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The 7th edition of the tumor, node, metastasis (TNM) staging system for lung cancer has five T categories for size: T1a, which is 2 cm or less; T1b, greater than 2 cm and up to and including 3 cm; T2a, greater than 3 cm and up to and including 5 cm; T2b, greater than 5 cm and up to and including 7 cm; and T3, tumors greater than 7 cm. These T categories are derived from an analysis of the staging database of the International Association for the Study of Lung Cancer (IASLC), which showed worsening prognosis for increasing tumor size.[1] That analysis was restricted to 8099 patients who had complete surgical resection of their disease, and who were node-negative, to avoid confounding the effect of size with the effect of lymph node involvement.

However, further analyses on 9007 patients who had undergone any type of resection (complete and incomplete) but whose tumors had no nodal involvement, and on 1,3742 patients with complete and incomplete resections and with tumors including any type of nodal involvement, showed that the tumor-size groups were consistent in all these populations.[1] In theory, size should also be important in patients who are treated for cure with radiotherapy or chemoradiotherapy. Size may be even more directly relevant for local control (without which cure cannot be achieved), because the surgeon who achieves an R0 resection is able to eradicate all clonogenic cells, regardless of the primary tumor size. However, in the case of radiotherapy, cell killing is proportional to dose, and

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The members of the IASLC Staging Committee and Participating Institutions have been listed in the Appendix.

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therefore, local control is dependent on both the number of clonogenic cells and the dose that can be safely administered. Indeed, a number of retrospective studies have suggested that tumor size is an important prognostic factor in lung cancer patients treated by nonsurgical means, particularly radiotherapy.[2–6] This is consistent with the hypothesis that larger tumors are likely to contain more clonogenic cells, and it fits with clinical observations of tumor size and local control using radiotherapy in other cancer sites.[7]

We therefore, undertook this study to see whether the T stage size categories derived from the surgical population for the 7th edition had a similar prognostic effect in patients from the same database but who were treated with radiotherapy with or without chemotherapy.

PATIENTS AND METHODS

The IASLC Staging Project was established in 1998 to inform the 7th edition of the TNM classification. A description of the project and the resulting database has been published previously.[8] More than 100,000 cases were accrued to the database and included patients treated by surgery, radiotherapy and chemotherapy, or combinations of these. To be eligible for the current analysis, patients on the database had to have a histologically confirmed diagnosis of NSCLC, no evidence of distant metastases, an intended treatment of radical radiotherapy (minimum 50 Gy) or combined chemotherapy and radiotherapy, no surgery, and an available tumor diameter . Other prognostic factor data including patient age, sex, performance status (ECOG), and weight loss were also drawn from the database. Unlike the initial analysis of the surgical patients, which was restricted to pathologically staged N0 cases, this analysis included patients with and without clinical lymph node involvement. Because the database was restricted to the era before fludeoxyglucose positron emission tomography became widely available, clinical diagnosis of lymph node involvement was unreliable. Further, the patients referred for radiotherapy were much more likely to have had lymph node involvement than surgical patients, and it would have been impractical to perform an analysis restricted to radiotherapy patients with negative nodes. However, it was intended that an adjustment for any effect of lymph node involvement would be undertaken through multivariate analysis, as it would be for other potential prognostic factors.

Statistical Analysis

The Kaplan–Meier estimator was used for survival curves. Survival was measured from the start of radiotherapy. Survival distributions were compared using the log-rank test. Univariate and multivariate Cox regression was used to model the effect of primary tumor size and other prognostic factors on survival. Stepwise variable selection was used to determine significant prognostic factors for the final multivariate model.

RESULTS

There were 868 patients from five separate sources available for analysis (Table 1). Patient characteristics are listed in Table 2. Survival of patients grouped according to size (T1, T2a, T2b, and T3) is shown in Figure 1. Patients with

TABLE 1. Patient Data Sources

Data Source	*n*	%
M.D. Anderson Cancer Center	241	27.8
National Cancer Institute of Canada	14	1.6
Peter MacCallum Cancer Center	130	15.0
Queensland Radium Institute	21	2.4
Radiotherapy Oncology Group (RTOG)	462	53.2
Total	868	100.0

TABLE 2. Patient Characteristics

Factor	Level	*n*	%
Tumor size, cm	PT size ≤ 3	233	26.8
	PT size > 3 and ≤ 5	297	34.2
	PT size > 5 and ≤ 7	175	20.2
	PT size > 7	163	18.8
Age, yrs	< 56	213	24.5
	< 64	223	25.6
	< 70	204	23.5
	≥ 70	221	25.5
	No data	7	0.8
Sex	Women	301	34.6
	Men	567	65.3
Performance status	0	478	55.1
	1	287	33.1
	2	44	5.1
	No data	59	6.8
Weight loss	< 5%	609	70.2
	≥ 5%	214	24.7
	No data	45	5.2
Chemotherapy	Chemotherapy	638	73.5
	No chemotherapy	153	17.6
	No data	77	8.9
Clinical T	T1a	69	8.0
	T1b	65	7.5
	T2a	271	31.2
	T2b	60	6.9
	T3	205	23.6
	T4	198	22.8
Clinical N	N0	158	18.2
	N1	43	5.0
	N2	545	62.8
	N3	122	14.1
7th editionTNM stage	IA	37	4.3
	IB	38	4.4
	IIA	19	2.0
	IIB	33	3.8
	IIIA	514	59.2
	IIIB	227	26.2

PT, primary tumor; TNM, tumor, node, metastasis; PS, performance status.

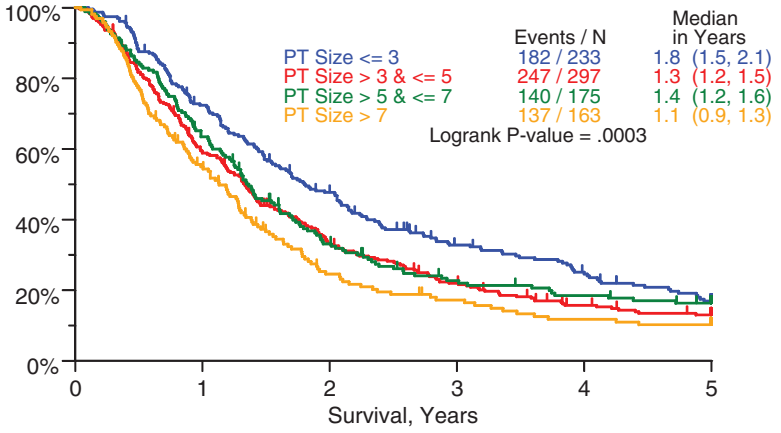

FIGURE 1. Survival according to PT size (cm). PT, primary tumor.

tumors less than or equal to 3 cm had significantly longer survival than patients with tumors larger than 3 cm but smaller than or equal to 7 cm. Patients with the largest tumors, that is, larger than 7 cm, had the worst survival, but this did not achieve statistical significance compared with T2b tumors ($p = 0.11$). Five-year survival above 10% was observed in all the four size categories. The influence of other prognostic factors is shown in Table 3. On univariate analysis, age, performance status, weight loss, chemotherapy, T category, and tumor size were all significant prognostic factors, but sex and clinical node status were not (Table 4). On multivariate analysis, age, weight loss, and tumor size equal to or less than 3 cm remained significant prognostic factors, but there was little evidence that size beyond this was prognostic (Table 5).

DISCUSSION

This analysis of the IASLC staging database is the first to study the relationship between survival and the tumor-size groupings of the TNM 7th edition in patients with NSCLC treated with radiotherapy instead of surgery. It reveals that patients with T1 tumors (7th edition) have longer survival than patients with T2 and T3 tumors categorized according to size, but it failed to provide evidence that there was a prognostic effect of size within the T2a and T2b categories. The survival of T3 tumor patients was shorter than for T2 tumor patients, but this did not achieve statistical significance. Five-year survival from the beginning of radiotherapy was similar for all four size groups, within the range of 10% to17% and all with overlapping 95% confidence intervals.

Several reasons can be advanced for the failure of this study to detect a convincing prognostic effect of tumor size beyond the T1 category. First, the population studied was different because unlike the surgical population, cases with involved nodes were eligible, and the effect of node involvement may have partly masked the effect of primary tumor size. That is, the worse prognosis conferred by node involvement and associated risk of distant metastasis overrode any adverse influence of increasing tumor size on local control as a competing risk for death. However, clinical N status overall was not in itself prognostic in this study, so this is unlikely to be the explanation for the absence of a prognostic effect of increasing tumor size beyond T1. In a previous publication based on the IASLC database, clinical N status was strongly prognostic, but this was driven mostly by the outcomes in patients who underwent surgical treatment.[9] The authors were unable to determine why clinical nodal status had little prognostic effect in nonsurgical patients, but suggested less effective treatment or the presence of comorbidities as possible explanations.

Second, it is possible that the prognostic effect of size varies according to the treatment given, that is, it is predictive rather than prognostic. As mentioned earlier, the size of the primary tumor may have different implications based on whether the cancer was removed surgically, or treated with (chemo)radiation. In the case of the surgically treated patient, increasing size (and with it the number of clonogenic cells) may be associated with increasing risk of distant metastasis, but may have little influence on technical resectability and local control. However, tumor size may be a major determinant of local control in the radiotherapy patient, if size is a surrogate for the number of clonogenic cells, and there is a limit to the dose of radiotherapy that can be given. It has been estimated that a 1-cm tumor contains 10^9 cells, a 3-cm tumor somewhere between 10^{10} and 10^{11} cells, and a 5-cm tumor a little over 10^{11} cells.[10] A 7-cm tumor contains approximately $10^{11.5}$ cells. Because cell killing by radiation is exponential, there should be a size–response effect for a fixed dose of radiation over the range of sizes represented by the T categories (assuming all the cells are clonogenic). The size of the effect should progressively diminish with increasing T size. The tumor may also be made up of stroma, inflammatory cells, and necrotic material as well as clonogenic cells, and intertumor variation in the proportions of these components may account for differences in response between tumors of similar size. Tumors also vary in their radiosensitivity, either an intrinsic genetically determined characteristic, or as a result of the presence or absence of tumor hypoxia. These factors, alone or in combination, may affect the probability of local control independently of the tumor size in an irradiated tumor, but not in one that has been resected. Finally, in this analysis no adjustment has been made for the prognostic effect of comorbidities, which are likely to be more important in a radiotherapy population compared with patients who are fit enough to undergo surgical resection.

A number of retrospective studies have analyzed the relationship between tumor size and survival in patients

TABLE 3. Survival According to Primary Tumor Size and Other Prognostic Factors

			Median 95% CI			5-Yr. Survival 95% CI	
Factor	**Level**	**Median Survival**	**Lower**	**Upper**	**5-Year Survival Estimate (%)**	**Lower (%)**	**Upper(%)**
Tumor size, cm	PT size ≤ 3	1.8	1.5	2.1	16.9	12.1	22.4
	PT size > 3 and ≤ 5	1.3	1.2	1.5	12.9	9.2	17.3
	PT size > 5 and ≤ 7	1.4	1.2	1.6	16.3	11.0	22.5
	PT size > 7	1.1	0.9	1.3	10.2	5.8	15.9
Age, yrs	< 56	1.4	1.3	1.7	17.2	12.1	23.1
	< 64	1.5	1.3	1.7	14.0	9.6	19.2
	< 70	1.5	1.3	1.8	14.2	9.4	19.9
	≥ 70	1.2	0.9	1.3	10.7	6.8	15.5
	No data	0.7	0.4	1.9	28.6	4.1	61.2
Sex	Women	1.6	1.3	1.7	16.2	11.9	21.0
	Men	1.3	1.2	1.4	13.1	10.3	16.3
Performance status	0	1.4	1.3	1.7	17.3	13.9	21.0
	1	1.3	1.2	1.4	10.0	6.6	14.2
	≥2	1.2	0.9	1.6	9.6	3.1	20.6
	No data	1.6	1.1	2.1	4.6	0.4	18.5
Weight loss	< 5%	1.6	1.4	1.7	16.6	13.5	19.9
	≥ 5%	1.0	0.8	1.2	8.7	5.3	13.1
	No data	1.2	0.9	1.6	7.8	2.1	18.4
Chemotherapy	Chemotherapy	1.4	1.3	1.6	16.3	13.3	19.6
	No chemotherapy	1.2	1.0	1.4	10.3	6.1	15.7
	No data	1.4	1.1	1.8	5.8	1.9	12.8
Clinical T	T1a	1.6	1.3	2.1	15.5	7.7	25.7
	T1b	2.6	2.1	3.2	22.6	13.0	33.8
	T2a	1.3	1.2	1.5	12.1	8.2	16.7
	T2b	1.3	0.9	1.9	16.9	8.4	28.0
	T3	1.3	1.1	1.4	13.3	8.9	18.6
	T4	1.3	1.2	1.4	14.0	9.2	19.9
Clinical N	N0	1.6	1.3	1.8	12.2	7.6	18.0
	N1	1.4	1.1	2.1	8.4	2.2	20.0
	N2	1.4	1.2	1.5	15.7	12.5	19.2
	N3	1.3	1.0	1.4	12.8	7.4	19.9
7th edition TNM stage	IA	2.0	1.5	2.9	16.2	6.6	29.6
	IB	1.3	0.8	1.8	2.6	0.2	11.8
	IIA	2.3	0.9	3.2	15.8	3.9	34.9
	IIB	1.7	1.3	2.0	15.2	5.5	29.2
	IIIA	1.4	1.2	1.6	15.6	12.4	19.2
	IIIB	1.3	1.2	1.4	13.0	8.7	18.1

PT, primary tumor; CI, confidence interval; TNM stage, tumor, node, metastasis stage; PS, performance status.

with nonmetastatic NSCLC treated with radiotherapy, with and without chemotherapy.[2–6,11,12] The largest study had 270 patients. All these studies demonstrated worse survival associated with increasing tumor size, but methodologic differences limit comparison with the present report. In none of the studies were the data analyzed according to the size groupings of the TNM 7th edition. Tumor size was sometimes treated as a continuous variable and sometimes as a dichotomous variable divided by the median value. In three studies, tumor size was calculated by adding the sizes of the primary tumor and the lymph nodes together.[4,5,11] Seven studies allowed the use of induction chemotherapy, and it is not always clear whether size was measured before chemotherapy, or after chemotherapy but before radiotherapy.[2–6,11,12] In the present study tumor size was measured before any treatment was given.

One prospective study of 509 patients treated with radiotherapy, with or without chemotherapy, assessed the effect of tumor volume on survival.[13] Size was analyzed both as a continuous variable and grouped by quartiles, and before any treatment was given. There were some similarities in the findings in that study and the present report. The smallest tumors in the lowest quartile had the best prognosis, but beyond that, the impact of size was less evident, as seen in the IASLC patients. Tumor size also had little effect on 5-year

TABLE 4. Univariate Analysis of Effect of Size and Other Prognostic Factors on Survival

Factor	χ^2	Degrees of Freedom	p^a
Age (continuous)	8.5413	1	0.0035
Age (quartiles)	11.4990	3	0.0093
Sex	2.2108	1	0.137
PS≥1	9.4579	1	0.0021
Weight loss < 5%	26.6417	2	<.0001
Chemotherapy	7.9419	2	0.0189
Clinical T	17.5764	5	0.0035
Clinical N	1.5727	3	0.6656
7th edition TNM stage	8.4642	5	0.1324
PT size (continuous)	13.6464	1	0.0002
PT size (grouped)	18.8680	3	0.0003

[a]*p* Value from likelihood ratio test.
PT, primary tumor; TNM stage, tumor, node, metastasis stage; PS, performance status.

TABLE 5. Multivariate Analysis of Effect of Size and Other Prognostic Factors on Survival

			95% Hazard Ratio CI		
Factor	**Reference Level for Hazard Ratio**	**Hazard Ratio**	**Lower Limit**	**Upper Limit**	*p*
Age (continuous) yrs	1-yr increase in age	1.014	1.006	1.022	0.0007
Weight loss ≥ 5%	Weight loss < 5%	1.492	1.259	1.769	<.0001
Weight loss not available	Weight loss < 5%	1.332	0.972	1.825	0.0744
PT size > 3 cm and ≤ 5 cm	PT size ≤ 3 cm	1.249	1.032	1.511	0.0223
PT size > 5 cm and ≤ 7 cm	PT size > 3 cm and ≤ 5 cm	0.973	0.791	1.197	0.9333
PT size > 7 cm	PT size > 5 cm and ≤ 7 cm	1.178	0.927	1.497	0.1681

PT, primary tumor; CI, confidence interval.

survival in both studies. The clinical implication of this last observation is that tumor size alone should not influence the decision to give radiotherapy with curative intent.

In summary, the effect of increasing tumor size on prognosis was less evident in patients treated with (chemo)radiotherapy (except for T1 patients) than for patients treated with surgery, or in most of the existing radiotherapy literature. This finding has been independently supported by the results of a prospective and methodologically rigorous cooperative group trial,[13] indicating that it is unlikely to be a chance finding. Therefore, this study alerts us to the possibility that the tumor size descriptors may not have the same applicability to patients treated by (chemo)radiotherapy as they do for patients treated surgically, at least, in terms of prognosis. Future editions of TNM will be informed by a prospective database that is actively accruing at the time of writing.[14] We hope the cases added to the database will provide sufficient numbers of patients in all treatment groups so that a broadly relevant staging system can be developed and used, regardless of which treatment is applied.

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APPENDIX

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