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Longevity after radiotherapy of stage III lung cancer: superior vena cava obstruction is associated with early mortality

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Background: People with locally advanced lung cancer have a poor prognosis. Physicians are unable to accurately predict life expectancy of patients. The aims of this retrospective study were to identify the life spans of individuals after radiotherapy of stage III carcinoma of the lung and to determine whether potential prognostic factors could identify people with distinct life spans.

Methods: Between September 1981 and August 2010, 133 consecutive individuals underwent definitive or palliative radiotherapy (with or without chemotherapy) for stage IIIA/IIIB disease. Analysis of the survival data revealed that 14 patients experienced long-term survival, exceeding 36 months; 94 patients had a short-term life span (STLS), extending between 4 and 36 months, and 25 patients were in the end-of-life (EOL) period, referring to the last 3 months of life. Recognized pre-treatment clinicopathological features were tested for their impact on prognosis.

Results: The largest proportion of patients presenting with superior vena cava obstruction (SVCO) ($P<0.001$) and receiving palliative radiotherapy ($P=0.009$) were from the EOL group. Most of the individuals with inadequate or no health insurance belonged to the STLS and EOL cohorts ($P=0.001$). Multivariate analysis revealed that the presence of SVCO was an independent factor predictive of shortened survival/EOL status ($P=0.001$).

Conclusions: Our study showed that a particular disease characteristic, health insurance status and provision of contemporary therapy can influence individual longevity. Selection and prioritization of health care resources remain important; therefore, identification of influential prognostic factors in lung cancer patients deserves further scrutiny.

Keywords: Radiotherapy; lung cancer; chemotherapy; prognosis

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Introduction

The incidence of stage III lung cancer is approximately 30% in a population-based cancer registry (1). The estimated overall 5-year survival rates are 14% to 25% for stage IIIA and 5% to 9% for stage IIIB non-small cell lung cancers (2). Although the prognosis for patients with locally advanced lung cancer (LALC) is not often in doubt, life expectancies (LE) can vary from days to years in this population. Available information is limited with regard to descriptions of life spans following radiation treatment of LALC. Moreover, there have been few published studies exploring influential factors associated with different life spans. It is in this context that we defined several periods of survival and attempted to characterize each category of longevity.

Methods

After obtaining approval from the institutional review board, an audit of the radiation oncology records was undertaken, and the cancer center database was queried for histologically-proven cases of lung cancer. Our retrospective review yielded a study population of 133 consecutive individuals treated between September 1981 and August 2010 for stage IIIA or IIIB lung cancer as defined in the revised American Joint Committee on Cancer (AJCC) staging system (3). All patients underwent pre- and post-treatment imaging studies (chest radiograph, computed tomography or positron emission tomography). Survival analysis showed that 25 people (19%) survived for 3 months or less; they comprised the end-of-life (EOL) group. Survival ranged from 4 to 36 months in 94 patients (71%), and they represented the short-term life span (STLS) cohort. Fourteen individuals (10%) had life spans between 44 months and 163 months; these individuals composed the long-term survival (LTS) category.

At our cancer center, concurrent chemoradiation for stage III lung cancer is usually practiced, but in five patients chemotherapy was sequentially administered because of poor performance status, superior vena cava obstruction (SVCO), small cell lung cancer histology or frail habitus. The chemotherapy treatment scheme involved the intravenous administration of cisplatin (50 mg/m^2 given on days 1, 8, 29 and 36) and etoposide (50 mg/m^2 given on days 1 to 5 and 29 to 33) for 4 cycles. The thoracic radiotherapy was megavoltage external beam fractionated irradiation. When the treatment intent was definitive, the total prescription dose was ≥60 Gy, given in 30 to 33 fractions; after 40 Gy, the spinal cord was excluded from irradiation. When the intrathoracic disease was considered too extensive for curative chemoradiotherapy, the treatment aim was for disease palliation, and the dose did not exceed 50 Gy; 30 Gy given in 10 fractions was usually applied. The supraclavicular area was included in the irradiated field when the primary lesion was located in the upper lobe or when suspected mediastinal or supraclavicular metastatic disease was demonstrated.

Follow-up data were obtained from a prospectively maintained, computerized database of the cancer center and from radiation oncology records. Clinical and radiological evaluations after treatment were performed by one or several staff physicians. The average interval from completion of radiotherapy to the first surveillance imaging was 3.6 months. Determinations of tumor status (regression, stasis, or growth) were made through side-by-side comparison of similar pre- and post-treatment imaging; the reviews were performed by the radiation oncologists in older cases and by the medical oncologists or pulmonary physicians during the later years of the study. Generally, after-treatment clinical examinations were requested at 3-month intervals during the first year, at 6-month intervals for the next 4 years, and annually thereafter. Tumor responses were evaluated and were scored according to the Response Evaluation Criteria in Solid Tumors (RECIST) method (4). A complete response was defined as the complete disappearance of the neoplastic lesion; a reduction in tumor size of at least 30% was considered a partial response. Progressive disease was indicated by an increase of at least 20% in the size of the lesion.

Survival was measured from the time of diagnosis of LALC until death or last contact. The Kaplan-Meier method and log-rank test were utilized to calculate and compare the survival rates associated with the three classes of longevity. Possible prognostic factors such as age, Eastern Cooperative Oncology Group performance status score, AJCC stage III subgroup classifications, tumor histologic subtypes, the presence or absence of comorbid illness or clinically manifested SVCO, the administration or omission of chemotherapy, the intent of radiotherapy (definitive or palliative), and the possession of adequate, inadequate or no health insurance were evaluated by comparative univariate analysis (chi-square or Fisher's test). The resulting significant factors were then tested, employing the multiple regression model, for their potential as independent predictors of short (≤3 months) survival. SAS version 9.4 (Cary, NC) was used for statistical computing, and $P<0.05$ was considered statistically significant.

Results

Patient and treatment characteristics

Out of 133 people in our study, 81 (61%) were men, and 52 (39%) were women. Individuals were classified according to specific age groups. There were two patients in the <20–30 years category, three patients in the 31–40 years category, 18 patients in the 41–50 years category, 56 patients in the 51–64 years category, and 54 patients classified as elderly (older than 64 years). *Table 1* shows that many individuals presented with an acceptable Eastern Cooperative Oncology Group performance status score of 0–1, (71%; 94 patients), stage

Table 1 Patient demographic, socioeconomic, clinicopathologic and treatment characteristics stratified according to longevity period

Features	LTS (n=14), n [%]	STLS (n=94), n [%]	EOL (n=25), n [%]	P value	
				Univariate analysis	Multivariate analysis
Age (years)				0.160	–
Non-elderly (<64)	7 [50]	53 [56]	19 [76]		
Elderly (≥64)	7 [50]	41 [44]	6 [24]		
Performance status score[¶]				0.120	–
0–1	12 [86]	68 [72]	14 [56]		
2–3	2 [14]	26 [28]	11 [44]		
Tumor stage*				0.640	–
IIIA	6 [43]	32 [34]	7 [28]		
IIIB	8 [57]	62 [66]	18 [72]		
Co-morbid illness[‡]				0.200	–
No	6 [43]	24 [26]	10 [40]		
Yes	8 [57]	70 [74]	15 [60]		
Tumor histology				0.330	–
NSCLC	12 [86]	79 [84]	24 [96]		
SCLC	2 [14]	15 [16]	1 [4]		
Chemotherapy				0.190	–
No	5 [36]	13 [14]	10 [40]		
Yes	9 [64]	55 [59]	5 [20]		
Unknown	0 [0]	26 [28]	10 [40]		
Radiotherapy				0.009	0.460
Definitive (≥60 Gy)	9 [64]	53 [56]	6 [24]		
Palliative (<60 Gy)	5 [36]	41 [44]	19 [76]		
Health insurance				0.001	0.780
Uninsured/underinsured[‡‡]	7 [50]	79 [84]	19 [76]		
Better insured[†]	6 [43]	5 [5]	1 [4]		
Not known	1 [7]	10 [11]	5 [20]		
Superior vena caval obstruction (SVCO)[ϕ]				<0.001	0.005
No	10 [71]	73 [78]	7 [28]		
Yes	4 [29]	21 [22]	18 [72]		

[¶], Eastern Cooperative Oncology Group scale; *, American Joint Committee on Cancer system; [‡], hypertension, diabetes mellitus, coronary artery disease, breast/thyroid/colon cancer, congestive heart failure, atrial fibrillation, liver cirrhosis, chronic obstructive pulmonary disease, hepatitis C, benign prostatic hypertrophy; [‡‡], Medicaid health insurance; [†], Medicare or private health insurance; [ϕ], adjusted odds ratio (OR) (SVCO presence *vs*. absence) =7.30, 95% CI for OR: 2.18–24.39. LTS, long-term survival; STLS, short-term life span; EOL, end of life; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

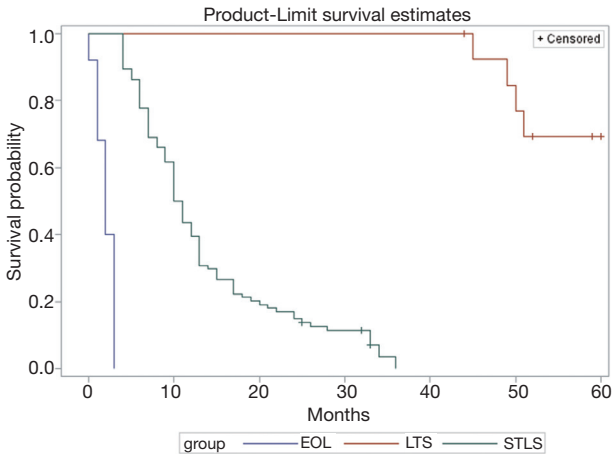

Figure 1 Survival by longevity classification. EOL, end of life (survival expressed as the last 3 months of life, n=25); LTS, long-term survival (survival which exceeded 36 months, n=14); STLS, short-term life span (survival between 4 to 36 months, n=94). P<0.001.

IIIB disease (66%; 88 patients) and comorbid illnesses (70%; 93 patients). The majority of lung cancer cases were not associated with clinically manifested SVCO (68%; 90 patients) and were of the non-small cell tumor subtype (86%; 115 patients). Of the 43 individuals with SVCO, 38 patients received palliative radiotherapy (PRT), two patients were treated with radical radiotherapy and three patients underwent radical chemoradiotherapy. Most of the studied subjects were uninsured or underinsured (79%; 105 patients). Furthermore, close to half of the individuals were non-elderly (59%; 79 patients) and received chemotherapy (52%; 69 patients) and definitive radiotherapy (51%; 68 patients). Among the 52 evaluable of the 133 individuals, the tumor response rate was complete, partial or absent in 17%, 77% and 6% of the cases, respectively. Subsequent disease progression occurred in 69% of the assessed patients. At the time of analysis, 12 patients were alive during a median follow-up of 55.5 (range, 25–163) months. There were 121 deceased individuals, and the median survival in this group was 10 months. The overall crude survival rates at 1, 2, 3 and 5 years were 36%, 14%, 7% and 2%, respectively.

Longevity periods and characterization analysis

The three longevity categories with corresponding survival rates are shown in *Figure 1* (P<0.001). As disclosed in *Table 1*, the non-small cell tumor histologic type and the presence of comorbid illness were found among most patients in the three longevity classes. Possession of better health insurance was more common among long-term survivors than EOL or STLS patients (P=0.001). Overall, there were only 12 patients with better insurance; none of these people received earlier care. Among the 14 long-term survivors, only six patients possessed better health insurance; among these, five individuals were treated with higher doses of radiation, and one subject received a lower dose. Also, two patients were diagnosed with stage IIIA disease, while four patients were diagnosed with stage IIIB lung cancer. Despite the fact that more of the younger patients were present in the EOL longevity category than in the other two classified longer life groups, those of the EOL cohort presented with a poorer performance status and more ominous stage IIIB disease. Moreover, fewer EOL subjects received chemotherapy and definitive radiotherapy. None of these observations with a negative implication potential reached statistical significance. On univariate analysis (*Table 1*), factors significantly predictive of poor prognosis were the presence of SVCO (P<0.001), receipt of PRT (P=0.009) and the possession of inadequate or no health insurance (P=0.001). However, on multivariate analysis, the only independent clinical characteristic indicating shortened survival/EOL status was the occurrence of SVCO (P=0.005).

Discussion

An accurate estimate of prognosis in individuals with advanced cancer is important to avoid futile therapy and unnecessary toxicity. Effective treatment applied to an a priori unfavorable cohort of patients may be erroneously interpreted as lacking benefit. We undertook this investigation because there are people who may survive longer than others, people whose LE is extremely short despite the application of standard of care therapeutic intervention, and people who are not suitable for state-of-the-art radical treatment but who are also judged not to have a very short life. Some physicians manage the disease in this last patient group with only a palliative intent, whereas others advocate a more intensive treatment regimen.

In this study, STLS represented the predominant longevity pattern after radiotherapy of LALC compared to the LTS or EOL situation, and this particular cohort proved difficult to characterize. From the literature, there is little information in this regard. We found that only

about 10% of the studied subjects were long-term survivors [an observation similar to the findings in other reports about people with treated lung cancer (1,5,6)]. Possession of better health insurance might have contributed to the improved prognosis, considering that most of these people received chemotherapy and definitive radiotherapy. In an investigation (7) to determine the influence of health insurance status on the outcome of 299,914 patients with non-small cell lung cancer registered in the National Cancer Database, payer status was found to be a significant predictor of overall survival. The uninsured and Medicaid patients had an increased risk of dying compared to those individuals with Medicare; the observed mortality rates were 36%, 21% and 17%, respectively. Forrest and colleagues (8) conducted a systematic review of the literature to determine whether socioeconomic inequalities in treatment occur and whether such circumstances affect mortality in people with lung cancer. The conclusion derived from the meta-analysis was that patients living in more deprived conditions were less likely to receive any type of therapy. In other studies of lung cancer patients treated with curative or palliative intent, a common clinical characteristic indicative of 5-year survival was the presentation of better performance status at the time of diagnosis and treatment (5,9,10).

Early mortality after radiotherapy for LALC is not uncommon. In the present experience, the 19% incidence of individuals in their last 3 months of life post-irradiation is higher than the 5% to 15% rate of occurrence noted by other investigators (11-14). Recent reports showed that early mortality was associated with poor performance status, increasing age, the presence of dyspnea, lower albumin and higher lactic acid dehydrogenase levels (11-17). In our view, EOL, as defined here and in several studies (11-19), indicates a phase in which directed therapy is no longer possible and the patient's condition declines. A determination of the reasons for early death is warranted so that ways to decrease such occurrences may be developed. During this period, symptom burden will increase and in the end, will become high. The quality of EOL care delivered to patients who die as a result of cancer is a major public health concern. It is not clear whether any treatment should be considered as a marker of poor quality EOL care. The literature (12,15,17,18) has shown that a significant proportion of patients died within a period of time too short to experience the additional benefit of PRT. Hence, it is believed that therapy applied in the last days or month of life is likely to provide minimal palliation or survival benefit. As a result, the concept of percentage of remaining life spent while receiving PRT has been proposed as a possible quality indicator of EOL care. Moreover, understanding what is important in the patient's terminal period is integral to the success of improving the care of the dying. In a study to determine factors considered important at the EOL, Steinhauser *et al.* (20) found that the participants ranked freedom from pain and dying at home as the most and least important, respectively. In the EOL situation, hospice has become the paradigm for high quality care because system-enrolled patients apparently consume less health care resources and generate less health care expenditures.

Our study demonstrated that the majority of patients experienced STLS following conventional treatment of LALC and also determined that SVCO is an independent predictor of shortened survival. Martins and Pereira (21) evaluated the correlation of clinical characteristics to survival in 1,635 patients with non-small cell lung cancer treated in Brazil. In their experience, the presence of superior vena cava syndrome (SVCS) in individuals with stage III disease was associated with a poor prognosis. Similarly, Gauden (22) retrospectively reviewed 249 patients treated by radiation for lung cancer-associated SVCS at the Queensland Radium Institute and found that the overall 2-year survival rate for the group was 5%. Our study has acknowledged limitations. Major drawbacks include the lack of documentation of clinical responses of SVCO to treatment and an inherent selection bias because this investigation was conducted in a retrospective fashion and all treatments were given at a single institution. We recognize that the approach to management of LALC evolved during the long period of our described experience. Currently, it is widely accepted that chemoradiotherapy has better value over radiotherapy alone, and that chemotherapy should be administered concurrently instead of sequential administration. Technological advances in radiotherapy have included intensity modulated radiation therapy; this improved technique of photon irradiation has enabled treatments with higher conformity and has allowed dose escalation to target areas with gross disease. Another limitation of our study is that these two contemporary management innovations were not used in most of our study participants. In our view, more evidence is needed to show the usefulness of molecular therapy, especially the prognostic implication of molecular features such as EGFR, ALK, PDL1. Also, how to select lung cancer patients with metastases who might derive benefit from

the early administration of therapy remains to be clarified.

Conclusions

LALC is generally an incurable disease condition. LE is a key to determine whether a patient has sufficient longevity to benefit from treatment. Because of consistent physician inaccuracy of LE estimates, several prognostic models have been developed to provide a more accurate prediction of life span of patients with advanced stage cancer. These prognostic indices, however, have been restricted to characterization and correlated with median survival. Reviewing long-standing practice, especially about different periods of survival after treatment, may constitute an important step towards measuring and improving outcomes of lung cancer care, especially to those who are near the EOL. Individual outcome is variable, and even the most favorable patient group contains people with very short, intermediate or long LE. Therefore, identification of longevity predictive features in LALC patients deserves further scrutiny.

Acknowledgements

None.

Footnote

Conflicts of Interest: This study was presented in part at the American Thoracic Society International Conference. May 19–24, 2017; Washington, D.C.

Ethical Statement: The study was approved by LSU Health Sciences Center-Shreveport Institutional Review Board (NO. 0347).

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