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CLINICAL INVESTIGATION **Lung**

PRETREATMENT PROGNOSTIC FACTORS IN PATIENTS WITH EARLY-STAGE (I/II) NON–SMALL-CELL LUNG CANCER TREATED WITH HYPERFRACTIONATED RADIATION THERAPY ALONE

Branislav Jeremić, M.D., Ph.D.,* Biljana Milicić, M.D., M.Sc.,* Aleksandar Dagović, M.D., M.Sc.,* Ljubisa Acimović, M.D., Ph.D.,† and Slobodan Milisavljević, M.D., M.Sc.†

Departments of *Oncology and †Surgery, University Hospital, Kragujevac, Serbia

Purpose: To investigate influence of various pretreatment prognostic factors in patients with early stage (I/II) non–small-cell lung cancer (NSCLC) treated with hyperfractionated radiation therapy alone.

Patients and Methods: One hundred and sixteen patients were treated with tumor doses of 69.6 Gy, 1.2-Gy, twice-daily fractionation. There were 49 patients with Stage I and 67 patients with Stage II. Eighty patients had Karnofsky performance status (KPS) 90–100 and 95 patients had <5% weight loss. Peripheral tumors were observed in 57 patients. Squamous histology was observed in 70 patients and the majority of patients had concomitant disease ($n = 72$).

Results: The median survival time for all patients was 29 months; 5-year survival was 29%. The median time to local progression and the distant metastasis were not achieved, whereas 5-year local progression-free and distant metastasis-free survivals were 50% and 72%, respectively. Multivariate analysis identified KPS, weight loss, location, histology, and the reason for not undergoing surgery as prognostic factors for survival. KPS, location, and histology influenced local progression-free survival, whereas only KPS and weight loss influenced distant metastasis-free survival.

Conclusions: This retrospective analysis identified KPS and weight loss as the most important prognostic factors of outcome in patients with early-stage NSCLC treated with hyperfractionation radiation therapy.

Prognostic factors, Non–small-cell lung cancer, Early stage, Radiation therapy, Hyperfractionation.

INTRODUCTION

There is a worldwide standard policy to offer surgery to patients with early-stage (I/II) non–small-cell lung cancer (NSCLC) (1–5). Still, however, there is a subset of patients who, although technically resectable, are not undergoing surgery because of comorbidity, age, or refusal. In these patients, radiation therapy (RT) alone has been considered the treatment of choice.

Recent years brought a number of important advances in this disease. Positron emission tomography became an important tool in staging of these patients, a tool more practiced in the treatment planning of lung cancer but in the posttreatment follow-up as well (6–8). Also, stereotactic single or fractionated dose RT was applied with local control rates of 80–100%, local recurrence-free survival rates of approximately 70% at 2 years, and 2-year survival of more than 60% (9–12). These results were accompanied with very rare ≥Grade 3 toxicity with median follow-up times in excess of 2 years.

A vast majority of reports, however, are on the use of conventionally planned radical RT. Numerous retrospective RT studies in the last four decades unequivocally have documented the outcome of patients with early (I/II) stage disease (13–43). Although one recent report (44) showed no advantage for RT over observation only, serious flaws in that report, both methodologic and statistical, raised the concern (45) that observation only should not be practiced in any case with early-stage NSCLC today. In addition, indirect evidence supporting active treatment came from the recent study (46) that showed that even tumors of small sizes of 6–15 mm, 16–25 mm, and 26–30 mm, when untreated, had 8-year fatality rates of 87%, 94%, and 88%, respectively.

Radiation therapy alone was capable of producing a median survival time of greater than 30 months (>40 months in T1N0) since the mid-1980s, with 5-year survival up to 30% in Stage I (40% in T1N0) and up to 25% in Stage II NSCLC (13–43). However, existing differences between studies regarding both pretreatment and treatment (RT) characteristics greatly obscure the findings. As a conse-

Reprint requests to: Branislav Jeremić, M.D., Ph.D., International Atomic Energy Agency, Wagramer Strasse 5, P.O. Box 200, A-1400 Vienna, Austria. Tel: (+43) 1-2600-21666; Fax: (+43) 1-26007; E-mail: b.jeremic@iaea.org

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quence, no firm conclusions can be made regarding the important RT issues such as the total dose deemed necessary for these tumors, use of elective nodal irradiation, or the influence of various pretreatment or treatment prognostic factors. In particular, these studies did not succeed in establishing prognostic factors in this disease treated with RT. The importance of prognostic factors is, therefore, rather difficult to evaluate without its verification in multiple studies because some of them may be significant by random chance alone. The characteristics of patients can influence their clinical course (47, 48). The magnitude of differences in outcome for categories of the strongest prognostic factors can be larger than those for the type of therapy used in various studies (49). Separation of patients into distinct prognostic subgroups should, therefore, represent an important contribution to the design and stratification in RT of early NSCLC trials and should enable the accrual of the individual patients in the more appropriate treatment groups or studies. Finally, this may also help correctly interpret the results of studies comparing different treatment regimens and help assess the potential of new treatment approaches.

We undertook the present analysis to identify potential prognostic factors in patients with early-stage NSCLC treated with RT. We have focused on clinical pretreatment prognostic factors, because they are easy to observe and note. They can be collected early in the course of the disease or diagnosis, before we decide on the "optimal" treatment approach in this disease and during the time of follow-up.

METHODS AND MATERIALS

Between 1988 and 1993, 116 patients with NSCLC at early stages (I and II) according to the International Staging System (3) were treated with hyperfractionation (Hfx) RT alone previously reported (27, 28). All these patients were subjects of the present retrospective analysis. In all cases, patients were, although technically able to be operated on, deemed unsuitable for surgery because of their concomitant medical problems (cardiovascular or pulmonary diseases) ($n = 72$) or because they refused surgery ($n = 44$). No patient underwent surgery and no patient received any form of adjuvant (chemo- or immuno-) therapy. All patients underwent pretreatment clinical staging including thoracic computed tomography scanning and bronchoscopy. No patient underwent mediastinoscopy. Performance status (PS) and weight loss were prospectively recorded before RT by involved radiation oncologist. Both protocols were originally approved by the local ethics committee and all patients gave consent.

Hyperfractionation RT regimen was introduced in both clinical Stage I and II NSCLC with total tumor doses of 69.6 Gy in 58 fractions in 29 treatment days (twice-daily fractionation) over 6 weeks. Two daily fractions of 1.2 Gy were used with an interfraction interval of 4.5–6 h. All fields were treated daily. The target volume for Stage I patients included the primary tumor and ipsilateral hilum with a 2-cm margin up to 50.4 Gy followed by the treatment of primary tumor only up to 69.6 Gy. For Stage II patients, the target volume included the primary tumor and ipsilateral hilum with a 2-cm margin and the ipsilateral mediastinum from the suprasternal notch to a level 6 cm below the carina (upper or middle lobe lesions) or to the diaphragm (lower lobe lesions), followed by the treatment of primary tumor and ipsilateral hilum up to 69.6 Gy. Doses were specified at mid-depth at the central axis for parallel opposed fields and at the intersection of central axes for other techniques. The maximum dose was 45.6 Gy to the entire heart, 60 Gy to the full circumference of the esophagus, and 50.4 Gy to the full circumference of the spinal cord. Two of 49 (4%) patients with Stage I and 6 of 67 (9%) patients with Stage II received total spinal cord (total circumference) doses of 51.60–54.00 Gy.

Tumors located maximally 5 cm from the midline were considered central, whereas those located more than 5 cm from the midline (and to the lateral chest wall) were considered as peripheral.

The follow-up procedures included laboratory and clinical tests including chest X-rays, and thoracic and upper abdominal computed tomography scanning, accompanied with other tests, if needed. The schedule for follow-up examination included examination at the end of treatment, every month for 6 months after the completion of treatment, every 2 months for 2 years thereafter, and every 4–6 months thereafter.

The RT-induced effects on normal tissues were assessed as either acute or late, according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer toxicity criteria (50).

Overall survival (OS) and relapse-free survival rates were calculated from the date of the start of Hfx RT by the Kaplan-Meier method, and differences between pairs of groups in survival curves were analyzed by the log–rank test. In calculating local progression-free survival (LPFS) or distant metastasis-free survival (DMFS) rates, patients who developed either type of failure were considered at risk for the other endpoint and censored at the time of last evaluation. The nodal failures were scored separately. The interaction of potential prognostic factors and their effect on OS, LPFS, or DMFS was analyzed using univariate and multivariate Cox analysis. All these statistical analyses were carried out by using the computer program SPSS (SPSS Inc., Chicago, IL).

RESULTS

Pretreatment patient and tumor characteristics are given in Table 1. All patients finished their treatment as planned. Only one patient was lost to follow-up. The median survival time for all patients was 29 months and 5-year survival was 29%. The median time to local progression was not achieved and 5-year local progression-free survival (LPFS) was 50.01%. The median time to distant metastasis was not achieved yet, whereas the 5-year DMFS was 72%.

Toxicity observed in these 116 patients included acute high-grade ($\geq$3) toxicity in 6 (5%) patients (bronchopulmonary, 3 patients; esophageal, 3 patients) and late high-grade toxicity in 6 (5%) patients (bronchopulmonary, 2 patients; esophageal, 3 patients; osseous, 1 patient). Because of toxicity, 11 (10%) patients had treatment interruptions ranging from 12 to 25 days (median, 17 days). All of these patients had comorbidities and no patient who refused surgery experienced such an event. No Grade 4 or 5 toxicities were observed and no spinal cord toxicity was observed.

Analysis of the pattern of failure showed that local recurrence was observed in 46 (Stage I, 18; Stage II, 28) patients and the distant metastasis in 29 (Stage I, 11; Stage II, 18)