

Comparison of curative and palliative radiotherapy efficacy in unresectable advanced non-small cell lung cancer patients with or without metastasis

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ABSTRACT

Objectives: To evaluate the efficacy of curative and palliative radiotherapy in inoperable advanced non-small cell lung cancer (NSCLC) patients with a performance status (PS) equal or greater than 2, and to compare the therapy effect on survival with or without metastatic disease.

Methods: From January 1998 through December 2004, 797 patients with inoperable stage III and IV NSCLC were treated with radiotherapy alone because of older age, cardiovascular disease, insufficient respiratory reserve or general frailty. Radical radiotherapy, consisting of approximately 60 Gy, given in 30 fractions was performed in 363 (45.5 %) of these patients. The other 434 patients (54.5%) were treated with palliative dose radiotherapy. Conventional follow-up of the patients was conducted at Izmir Oncology Center. All results were evaluated statistically.

Results: Seven hundred and sixty-three patients (95.7%)

were male. The mean age was 61.02 years (\pm 9.678), ranging from 30-88 years. The prominent histology was squamous cell carcinoma (70.7%). Sixty-five patients (8.2%) have been staged IIIA, 419 (52.6%) IIIB, and 313 (39.3%) IV. The median follow up of patients was 274.19 days. One-year survival rate was 37%, and 2-year survival rate was 11% in the radical radiotherapy group, while these rates were 20% and 5% in the others.

Conclusion: Although radical thoracic radiotherapy for metastatic NSCLC has not been adopted universally, this study shows that curative radiotherapy for the primary tumor provides additional survival benefit in patients with metastatic disease compared with palliative radiotherapy. This result raises the question of whether treatment with radical radiotherapy alone might be the most beneficial and cost-effective treatment of advanced stage NSCLC.

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The incidence of lung cancer is declining following a drop in smoking rates, but it is still the leading cause of death from cancer worldwide, and survival rates are poor everywhere.¹⁻³ Approximately 5% of people with lung cancer survive for 5 years, and nearly all of these are cured by surgery after

fortuitously early diagnosis.¹ For patients with stage I or stage II non-small cell lung cancers (NSCLC), surgical resection with adjuvant chemo- radiotherapy is considered the standard of care.³⁻⁵ Unfortunately, most lung cancers are of considerable size when first detected, and approximately 80% are inoperable

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as a result of extensive local spread, or distant metastases.^{2,6} Although the standard regimen for advanced disease cannot yet be defined, the benefits of cisplatin-based chemotherapy and of combination chemoradiotherapy have been established for treating of stage III-IV NSCLC.⁷⁻⁹ This therapy is currently recommended as the preferable treatment for patients with advanced NSCLC, but its benefit seems limited to fit patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.^{8,9} In spite of all advances in therapy, life expectancy at the time of diagnosis in patients with lung cancer is less than 2 years.⁶ Conflicting results obtained from previous randomized trials indicate which therapy policy is preferable in terms of survival and quality of life, and which combination therapy regimen provides additional survival benefit in advanced disease.^{1,7-10} Despite substantial evidence that cisplatin-based chemotherapy may provide only small benefit in survival, leads to deterioration in quality of life, and is highly cost ineffective in advanced NSCLC, most patients are treated with combination chemo radiotherapy regimens, and thoracic radical radiotherapy has been regarded as the treatment for local control or palliation of disease.¹¹⁻¹⁴ In the present study, we included 797 patients with stage III-IV NSCLC who had been treated with radiotherapy alone because of older age, cardiovascular disease, insufficient respiratory reserve or general frailty, and analyzed our experience with these patients to better define the potential benefit of curative radiotherapy. In addition, we compared the efficacy of radical and palliative radiotherapy on survival. We tried to emphasize whether radical radiotherapy may be preferable for treating patients with advanced stage NSCLC and what is the best therapy to administer them.

Methods. This study was conducted at the Izmir Oncology Center from January 1998 to December 2004. Seven hundred and ninety-seven patients with a diagnosis of stage III or IV NSCLC, no previous surgery or chemotherapy, and an ECOG PS equal or greater than 2 were investigated. All patients were treated with radiotherapy alone, and patients who received adjuvant or concomitant chemotherapy were excluded. Three hundred and sixty-three patients with unresectable NSCLC, whose tumors were confined to the thorax were selected for immediate, radical radiotherapy consisting of 60 Gy (range 54-72) given in 30 fractions of approximately 2 Gy daily, 5 days a week, over a period of 6 weeks, aimed at cure or prolonging survival. For the remaining patients, initial distant metastatic disease, or poor performance

status precluded such potentially curative treatment. These 434 patients received several fractions of radiotherapy for palliation of thoracic symptoms or metastases. Either a Cobalt-60 unit or a linear accelerator (6 MV photons) was used to treat the patients. The target volume generally included the primary tumor as well as regionally involved nodes. Custom blocks were used in most fields to minimize normal tissue involvement. In most cases, the anterior-posterior field technique was used to deliver up to 40 Gy; then oblique or multiple fields were used to complete irradiation up to 66 Gy. All 797 patients were routinely seen in the Izmir Oncology Center for 7 years. Conventional follow-up consisted of routine outpatient appointments (one post-treatment, then appointments at 3 monthly intervals in the first year, and 4 monthly intervals over the following years) for medical assessment and investigations to monitor disease progression. Patients were also seen based on need. In December 2004, the last contact with all patients was made by telephone or mail for information of their status. All results were evaluated statistically. Pearson correlation analysis, Kaplan Meier method for survival curves and Log-rank test for the comparison between groups were performed for statistical analysis. P-values less than 0.05 were considered statistically significant. Descriptive and frequencies of the parameters were also evaluated.

Results. Seven hundred and sixty-three patients (95.7%) were male, and 34 (4.3%) were female. The mean age was 61.02 years (\pm 9.678), ranging from 30-88 years. All patients had pathologically proven NSCLC unfit for surgery because of disease extension or co-morbidity. The PS was 2 in 604 patients (75.7%) and 3 in 193 patients (24.3%). The prominent histology was squamous cell carcinoma (70.7%). In 505 patients (63.4%), primary tumors were localized in the superior lobes, and in 470 (58.9%) these were in the lobes of the right lungs. Distant metastases were determined in 313 (39.3%) of all patients. According to the stage grouping of the 1997 TNM Staging System, 65 patients (8.2%) have been staged IIIA, 419 (52.6%) IIIB, and 313 (39.3%) IV. The median follow up of patients was 274.19 days with a range of 1-1710 days (**Figure 1**). Four hundred and sixty-six (58.5%) patients died, while 49 patients (6.1%) were alive at the end of the study. Two hundred and eighty-two patients (35.4%) were lost to follow-up, and survival times of these patients were estimated according to the last appointments. The majority (84.8%) of patients received thoracic radiation according to the RTOG 93-09 (intergroup 0139) trial. In addition, in 149 of these patients (18.7%) radiotherapy was also

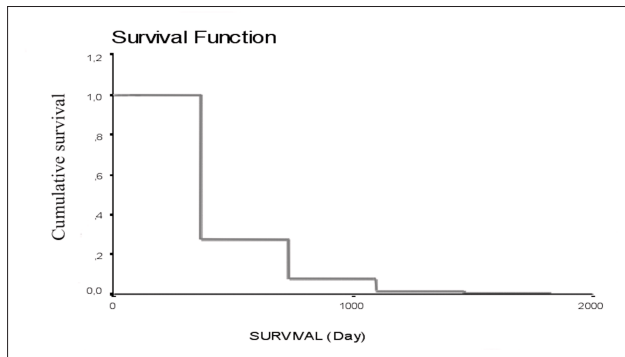


Figure 1 - Cumulative overall survival curve of patients.

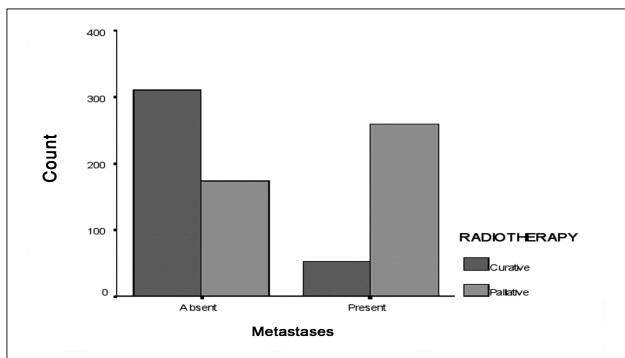


Figure 2 - Distribution of the cases according to presence of metastases and application regimen of radiotherapy.

Table 1 - Dose- and radiotherapy regimen-related survival.

Dose level (Radiotherapy regimen)	4-72 Gy Curative n=363	3- 45 Gy Palliative n=464
Cumulative median survival (days)	338.2	220.6
Survival time (%)		
6 months	61	42
12 months	37	20
24 months	11	5
≥5 years	0.5	0.3

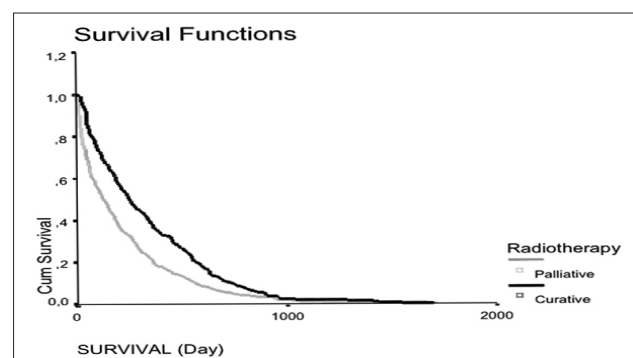


Figure 3 - Survival curves of the patients treated with curative and palliative radiotherapy in 1710-day follow up ($p<0.0001$).

performed at metastases. The remaining 121 patients (15.2%) received several fractions of radiotherapy for palliation of metastases and in these patients, radiotherapy was not performed at primary tumors (Figure 2). In the radical radiotherapy group, 42/363 patients (11.6%) died before radiotherapy was completed. Dose and radiotherapy regime related survival rate of the patients are summarized in Table 1. Log-rank analysis (Figure 3) showed that curative radiotherapy provides additional survival benefit in all patients compared with palliative irradiation ($p<0.0001$). In Pearson Correlation analysis, there was a statistical significance between survival and applied radiotherapy regimen ($p=0.007$).

Discussion. The therapy management of NSCLC has been the focus of extensive investigation over the last decade, and several new strategies are currently being investigated to improve the survival of advanced disease. Nonetheless, existing therapy strategies are suboptimal for all stage groupings. The only exception is complete resection for stage 1A in which a cure is achieved in 70-85% of patients.^{12,15-17} In the other operable stage groupings, published data suggest that

cisplatin-based chemotherapy after radical surgery may increase 5-year survival from approximately 50% by a further 5%, but the confidence interval for this estimate is too wide for a firm conclusion.¹² In our series, the percentage of ≥ 1 -year survival of stage IIIA disease was 40%, and ≥ 2 -year survival 7.7%. Although stage IIIA disease can be regarded as an operable stage in some circumstances, expectancy of survival was always much less than stage I and II disease.^{4,5} In the present study, any patients with stage IIIA did not undergo surgical treatment, and 5-year survival was not determined. Many treatment options exist for treating inoperable NSCLC. The choice of treatment depends on the histologic type and stage of disease, presence or absence of metastases, underlying health of the patients, degree of symptoms and the bias of the treating physicians. Therapy regimens include systemic chemotherapy, irradiation of primary tumor, or metastases, adjuvant and prophylactic cranial radiotherapy, as well as medication for pain or other symptoms.^{12,15-19} However, in most of these options, the aim is palliation of symptoms because advanced stage NSCLC is accepted as a non-curable disease. Radiotherapy is also regarded as the treatment for

local control of NSCLC. Platinum-based combination chemotherapy is applied for systemic control in these patients. Unfortunately, all treatment regimens continue to show only modest improvement in outcome and their effects remain small for patients with metastatic NSCLC.^{12,15-19} In addition, the benefits of most treatment schedules seem limited to fit patients with better PS. The published data reports that the 5-year survival rate for patients with advanced stage NSCLC still remains <1%. Similarly in the present study, survival rate was poor at 0.62% for all patients. Recently Sorensen et al,¹² evaluated the scientific literature on chemotherapy trials in patients with NSCLC. This systematic review covered 53 publications including 6 meta-analyses based on 65 prospective randomized trials comprising 15607 patients, and an additional 32 prospective randomized studies including 8902 patients. This paper demonstrated that cisplatin-based chemotherapy confers a modest, median 1.5-3 months, prolongation of survival in stage III-IV disease. The authors also noted that the use of chemotherapy was not available for elderly patients, and for patients in poor general condition. Based on increasing understanding of cancer cell biology, new drugs for NSCLC have been developed over the past decade. These were reported to provide additional survival benefit in advanced disease, and to be less toxic strategy for treatment of NSCLC compared with earlier cisplatin-based regimens. The most important handicap of this therapy with these agents is high price originating from an increase in product cost.¹²⁻¹⁶ In a review article, Clegg et al¹ examined the clinical effectiveness and cost-effectiveness of 4 new drugs in NSCLC. Three of them are used for first-line treatment, while the other is used only after first-line chemotherapy has failed. It was reported that the gains in duration of survival with the new drugs were only a few months. In this review, the cost-effectiveness of these drugs was not calculated because the available data did not provide an entirely satisfactory basis for this calculation. The authors suggested that the main problem was the lack of the direct comparisons of new drugs, and large-scale prospective randomized trials are necessary to confirm the benefit on survival of these agents. In our series, radical radiotherapy for the primary tumor confers median 117.6 days in stage III-IV disease compared with palliative irradiation. Moreover, therapy tolerance was good in all patients.^{1,12,16,17} In many reports, chemo-radiation schedules having been shown to impact on response and survival compared to radiation alone in a selected patient population. However, in these reports, therapy benefits for some populations, such as elderly patients and patients

with poor performance status, are underrepresented. If it is emphasized that half of all lung cancer occurs in persons aged 65 years, it is easily estimated how difficult it is to decide therapeutic approach, and to achieve the right balance between expected benefits of treatment and potential toxicity. Moreover, increasing age seems to be the most important determinant of receiving chemotherapy or not. The elderly patients are more likely to be given only supportive care or no therapy.^{8,10,14-19} In our study, most patients were of older age, with 87.3% ≥ 50 , and 59.8% ≤ 60 . Since the risk of serious complications from radiation therapy is smaller than chemotherapy, only radiation therapy was applied. In most patients, chemotherapy was not preferred because of older age. The remaining younger patients had a cardiovascular disease, insufficient respiratory reserve or general frailty. Their PS scores were >2 . Therefore, all patients were treated with radiotherapy alone. A number of studies demonstrated that radiation therapy may be safely delivered to elderly patients, or advanced NSCLC patients with poor PS.²⁰⁻²² The radiation therapy option may overcome many of the performance- and age-related drawbacks, which prevent more aggressive and toxic therapies. Tombolini et al²⁰ suggested that radiotherapy is a good management for advanced NSCLC in all patients assuring good quality of life, high rates of relief of symptoms and overall survival similar compared with chemotherapy and chemotherapy plus radiotherapy. Similarly, during therapy, serious complications were not determined in any of the patients in our series, and this result confirmed that radiation therapy may be safely delivered to all patients with advanced NSCLC at not merely palliative doses, both to achieve better local control and to give likely survival benefits.^{14,20-22} There are limited studies available on only radiotherapy (without chemotherapy) treated patients with advanced staged NSCLC. Generally, most reports comprise chemo-radiotherapy schedules. The low PS patients, such as PS2, usually account for a small proportion of patients enrolled in trials but represent a significantly higher portion when population based surveys are conducted. Gridelli et al,⁸ mention a meta-analysis evaluating the efficacy of chemotherapy in patients with advanced NSCLC. In this report, cisplatin-based chemotherapy has shown statistically significant survival advantage over supportive care. However, the benefit achievable has seemed more evident for fit patients (PS 0 or 1) and there was no consistent evidence on the real efficacy and the real damage of chemotherapy for PS2 patients. Recently, Norsa et al¹⁰ claimed that the best therapy for PS 2 or 3 patients might be treatment

with some supportive agents such as somatostatin, retinoids, melatonin, vitamin D, bromocriptine and cyclophosphamide.⁸⁻¹⁰

In the present study, we determined that curative radiotherapy provides an additional survival benefit in metastatic disease compared with palliative irradiation, and observed the statistical significance between survival and applied radiotherapy regimen. We also believe that curative thoracic radiotherapy for advanced NSCLC is the most beneficial and cost-effective treatment in terms of survival, side-effects of treatment and quality of life within the limits of this study. In conclusion, it was apparently seen that the pace of therapy progress for lung cancer is too slow and it does not seem promising for the near future. Therefore, until the most beneficial and cost-effective, as well as the least toxic, therapeutic agents are developed, curative tumor irradiation may be preferred for the therapy of all patients with advanced NSCLC.

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