

Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2009 April 1; 73(5): 1383–1390. doi:10.1016/j.ijrobp.2008.06.1935.

The Effect of Radiation Dose and Chemotherapy on Overall Survival in 237 Patients with Stage III Non-Small Cell Lung Cancer

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Abstract

Purpose—To study the effects of radiation dose, chemotherapy and their interaction in patients with unresectable or medically inoperable stage III non-small cell lung cancer (NSCLC).

Methods and Materials—A total of 237 consecutive stage III NSCLC patients were evaluated. Median follow-up was 69.0 months. Patients were treated with radiation therapy (RT) alone (n = 106), sequential chemoradiation (n = 69) or concurrent chemoradiation (n = 62). The primary endpoint was overall survival (OS). Radiation dose ranged from 30 to 102.9 Gy (median 60 Gy), corresponding to a bioequivalent dose (BED) of 39 to 124.5Gy (median 72 Gy).

Results—The median OS of the entire cohort was 12.6 months, and 2- and 5-year survival rates were 22.4% and 10.0%, respectively. Multivariable Cox regression model demonstrated that Karnofsky performance status ($P = 0.020$), weight loss $< 5\%$ ($P = 0.017$), chemotherapy (yes vs. no), sequence of chemoradiation (sequential vs. concurrent) ($P < 0.001$) and BED ($P < 0.001$) were significant predictors of OS. For patients treated with RT alone, sequential chemoradiation and concurrent chemoradiation, median survival was 7.4, 14.9 and 15.8 months, and five-year OS was 3.3%, 7.5% and 19.4% respectively ($P < 0.001$). The effect of higher radiation doses on survival was independent of whether chemotherapy was given.

Conclusion—Radiation dose and use of chemotherapy are independent predictors of OS in stage III NSCLC, and concurrent chemoradiation is associated with the best survival. There is no interaction between RT dose and chemotherapy.

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The study has been presented in 49th ASTRO, October 30, 2007, Los Angeles as an oral presentation. It has been regarded as *Best of ASTRO 2007* and was asked to be quoted in 3rd Annual Mid-Atlantic ASTRO Review Course on January 10, 2008, the University of Maryland*s.

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Keywords

NSCLC; Stage III; Dose; Chemotherapy; Radiation

Introduction

In 2007, there were an estimated 213,380 new cases and 160,390 deaths of lung cancer in the United States (1). The majority of them are locally advanced non-small cell lung cancer (NSCLC). The standard care for locally advanced unresectable stage III NSCLC is combined modality therapy with chemotherapy and radiation therapy (RT). Despite improved survival with combined modality therapy (2, 3), local-regional recurrences and the development of distant metastases are still problematic and the prognosis of the majority of patients remains poor. Recent trials suggest that local-regional control can be improved with RT dose escalation and that this improvement in local-regional control could be translated into an overall survival (OS) benefit (4-8). Several studies have suggested that radiation dose is a significant prognostic factor for tumor control and OS in patients with locally advanced or medically inoperable early-stage NSCLC. A prospective dose-escalation trial at our institution showed a positive relationship between dose and local-regional tumor control, as well as OS, with RT doses in the range of 63 to 103 Gy in patients with stage I-III NSCLC largely treated with RT alone (9). Radiation dose was the only significant factor affecting both local tumor control and OS for patients with stage I-III disease in our trial (9, 10). In a series of 114 patients with stage I-II NSCLC, we have recently confirmed the positive dose effect in early stage NSCLC and demonstrated that high-dose radiation (higher than 66 Gy in 2 Gy fractions) is more important for patients with larger tumors (> 4cm) (11). Using 3-D conformal techniques, recent studies have demonstrated the safety of high dose radiation in patients with unresectable or medically inoperable stage III NSCLC treated with radiation alone or neoadjuvant chemotherapy plus radiation, provided that normal structure dose-volume limits are not excessive (4-10, 12). Researchers from the University of North Carolina reported that doses of 74 Gy (13, 14) and 90 Gy (15) can be delivered safely with induction chemotherapy followed by concurrent chemoradiation.

In this study, we aimed to investigate the effects of radiation dose and chemotherapy on OS and determine if the radiation dose effect is independent from that of chemotherapy in patients with unresectable or medically inoperable stage III NSCLC

Materials and Methods

Patient Selection

This is an Institutional Review Board approved retrospective study. Eligible subjects included all patients with stage III NSCLC registered in the radiation oncology database and treated with radiation-based therapy at University of Michigan Hospital (UM) and the Veterans Affairs Ann Arbor Healthcare System (VA) between January 1992 and July 2004. Patients treated with preoperative and postoperative radiation or for recurrent disease were excluded. All 237 patients included in this study were restaged according to American Joint Cancer Committee (AJCC) 2002 criteria: stage IIIA (T1-3N2M0, T3N1M0) and IIIB (T1-3N3M0, T4N0-3M0). The Charlson scoring system was used to assess the degree of comorbidity (16). Consistent 3-D conformal techniques were used throughout the study period. Positron emission tomography (PET) staging was based on physician's preference at University of Michigan Hospital; and it was routinely not performed at the Veterans' hospital during the study period. A total of 75 patients (55 at UM and 20 at VA) underwent PET scan.

General Treatment Decision

Treatment decisions were generally made by an institutional tumor board consisting of thoracic surgeons, medical oncologists, and radiation oncologists. Treatment strategies were determined based on tumor status and a patient's performance status and co-morbidities. Most of the patients with stage III NSCLC were treated with RT with definitive or palliative intent either with or without chemotherapy based on the time of treatment (more concurrent chemoradiation in recent years) and the decision of the treating physicians based on the patient's candidacy for chemotherapy.

Radiation Therapy Technique

CT simulation guided 3D plans were used throughout the study period. Intensity modulated radiation therapy was not utilized for the treatment of lung cancer, the planning techniques and dose calculation algorithm were unchanged during the study period. Patients who enrolled into the dose escalation protocol received RT based on the following protocol specifications, which has been described previously (9, 11). The fraction size was 2.1 Gy for protocol patients. For patients who received radiation in the off-protocol setting, the radiation technique was similar to protocol patients, except that fraction size ranged from 1.8 Gy to 3.0 Gy.

Data Analysis and Statistical Considerations

OS was the primary endpoint of this study. Survival was defined as the duration between the dates of pathological diagnosis and death. Age at diagnosis, gender, Karnofsky Performance Score (KPS), percent of total body weight loss (< 5 vs. ≥ 5%), smoking history (yes vs. no), pre-RT oxygen use (yes vs. no), non-malignant pleural effusion (yes vs. no), disease stage (IIIA vs. IIIB), Charlson's comorbidity score, RT dose, gross tumor volume (GTV), on-protocol vs. off-protocol, chemotherapy use (yes vs. no) and timing of chemoradiation (sequential vs. concurrent) were collected from original medical records and assessed for their impact on survival. To further study the radiation dose effect, biological equivalent dose (BED) was estimated for every patient using an α/β ratio of 10.

Data were considered right-censored for OS outcomes if no events occurred by the end of follow-up. Cox's proportional hazards model was used for multivariate analysis to estimate the simultaneous impact of clinical factors on OS, and to test the significance of the interaction between BED and chemotherapy in terms of OS. The Kaplan-Meier method was used to estimate survival curves for different groups, and the Log-Rank test was used to determine whether there were significant differences between groups in terms of the survival curves. All *P* values were two-sided, with *P* < 0.05 considered significant.

Results

Patient and Treatment Characteristics

Characteristics of all 237 patients are provided in Table 1. A total of 106 patients were treated with RT alone, 69 with sequential chemoradiation and 62 with concurrent chemoradiation. The agents commonly used for chemotherapy were carboplatin, etoposide, paclitaxel, cisplatin and vinorelbine. For sequential chemoradiation, 24 patients were treated with carboplatin and paclitaxel, 19 with cisplatin and vinorelbine, 6 with cisplatin and etoposide and 20 with other regimens. For concurrent chemoradiation, 21 patients were treated with carboplatin and etoposide, 18 with cisplatin and etoposide, 17 with carboplatin and paclitaxel and 6 with other regimens. Thirty-one patients were enrolled in the radiation dose escalation protocol and 206 patients were treated off-protocol. GTV data were retrievable for only 101 patients.

The radiation dose for the whole group ranged from 30 Gy in 3 Gy fractions to 102.9 Gy in 2 or 2.1 Gy fractions, with a median dose of 60 Gy in 2 Gy fractions. The median BED was 72.2 Gy (range: 39-124.5 Gy). There were 169 patients treated with definitive radiotherapy and 68 with palliative dose of radiotherapy. The median BED was 78 Gy (95% CI of 77-79 Gy) for patients treated with definitive intent and 50 Gy (95% CI of 47-53 Gy) for patients treated with palliative intent. These dose distributions were too narrow to allow further meaningful analysis for these groups individually.

Overall Survival

Median follow-up was 69.0 months (range, 0.2-146). The median OS for the whole group was 12.6 months (95% CI: 10.5-14.7 months, range: 0.8-153.2 months). The two and five-year OS were 22.4% and 10% respectively. Figure 1A shows the OS of the entire group. The median OS for patients treated off-protocol ($n = 206$) and those within the dose escalation protocol ($n = 31$) were 12.1 months (95% CI: 9.7-14.5 months, range: 0.8-153.2 months) and 15.6 months (95% CI: 9.6-21.5 months, range: 4.8-107.6 months) respectively; two and five-year OS were 22.3%, 9.7% and 16.1%, 6.5% respectively. There was no significant difference for OS between the protocol and off-protocol groups ($P = 0.825$).

Factors Associated with OS - Univariate analysis

The effects of patient characteristics, tumor factors and treatment parameters on OS are shown in Table 1. Univariate analysis demonstrated that higher KPS (HR 0.965, 95% CI: 0.935-0.996, $P = 0.029$), $< 5\%$ of total body weight loss (Figure 1B, $P < 0.001$), PET scan before treatment ($P = 0.044$) and use of chemotherapy (Figure 2A, $P < 0.001$) were significantly associated with improved OS. There were no significant differences in OS based on gender, smoking history, or pre-RT oxygen use ($P = 0.093$ for all factors). Neither advanced age nor higher co-morbidity score was associated with worse OS ($P_{all} = 0.245$).

The number of patients who received definitive RT for stage IIIA and IIIB disease were 86 (84.3%) and 83 (61.5%) respectively ($P < 0.001$). There was a trend for difference in OS between patients with stage IIIA and IIIB disease. The median, two-year, and five-year survivals were 14.1 months (95% CI: 11.7-16.6 months, range: 1.7-129 months), 26.5%, and 9.7% for patients with stage IIIA disease, and 11.1 months (95% CI: 9.2-13.0 months, range: 0.8-153 months), 17.8% and 8.8% for patients with stage IIIB disease ($P = 0.089$). The presence of a non-malignant pleural effusion was not a significant factor for OS ($P = 0.181$). GTV was not significantly associated with OS when analyzed as a continuous variable ($P = 0.447$) or as a categorical variable based on the median value ($P = 0.619$).

In terms of treatment variables, increasing BED was associated with improved OS (HR 0.972, 95% CI: 0.962-0.981, $P < 0.001$) in the entire group. The median survival for patients treated with RT alone, sequential chemoradiation and concurrent chemoradiation were 7.4 months (95% CI: 5.3-9.5 months, range: 0.8-152 months), 14.9 months (95% CI: 13.2-16.7 months, range: 2.2-132.2 months) and 15.8 months (95% CI: 11.2-20.4 months, range: 4.2-153.2 months); and five-year OS were 3.3%, 7.5% and 19.4%, respectively ($P < 0.001$). Figure 2B shows OS in different treatment groups.

Factors Associated with OS – Multivariate analysis

To further evaluate the independent effect of patient characteristics, tumor factors and treatment parameters on OS, a multivariate Cox proportional hazards regression analysis was performed (Table 2). This analysis included those factors with $P \leq 0.1$ from univariate analysis. As a consequence, KPS, weight loss $< 5\%$, pre-RT oxygen use (yes vs. no), stage IIIA vs. IIIB, PET scan before treatment, addition of chemotherapy, sequence of chemoradiation, and BED were included as covariates in the Cox regression model.

Higher KPS ($P=0.020$) and weight loss $< 5\%$ of total body weight ($P=0.017$) remained significantly correlated with improved OS on multivariate analysis. However, neither pre-RT oxygen use ($P=0.215$), lower disease stage (IIIA vs. IIIB) ($P=0.677$) nor PET scan before treatment ($P=0.327$) was associated with OS.

Radiation dose remained a significant factor on multivariate analysis. The hazard ratio of BED for death was 0.976 per Gy (95% CI: 0.966-0.985, $P<0.001$). The relationship between BED and OS is shown in Figure 3. Figure 3A depicts the BED distribution of different treatment regimens, while Figure 3B shows OS over radiation dose for each patient. Although the narrow BED distribution did not allow stratified analysis within each treatment group, a significant dose-response relationship was seen between BED as a continuous variable and survival ($P<0.001$).

The sequence of chemoradiation remained a significant prognostic factor. Concurrent chemoradiation ($P<0.001$) and sequential chemoradiation ($P=0.025$) were both associated with significantly better OS than RT alone (Table 2). Further comparing the effects of concurrent and sequential chemoradiation revealed that concurrent chemoradiation was associated with a significantly better prognosis than sequential chemoradiation ($P=0.034$).

Interaction between Radiation Dose and Chemotherapy

To investigate whether there was a significant interaction between radiation dose and chemotherapy, the product of BED and chemotherapy (BED*CHEMO) was included as a covariate in the Cox model. No significant interaction was confirmed between BED and chemotherapy (HR = 1.013, 95% CI: 0.993-1.034, $P=0.200$) (Table 3). This suggests that radiation dose and chemotherapy were independent factors for OS, and the impact of BED on survival outcomes did not vary by the administration of chemotherapy.

The hazard ratio of BED for death was 0.973 per Gy (95% CI: 0.962-0.985, $P<0.001$) in patients treated with RT alone and 0.979 per Gy (95% CI: 0.962-0.996, $P=0.015$) in patients treated with chemoradiation.

Discussion

The radiation dose effect in NSCLC has been reported previously, mostly in the context of stage I/II NSCLC (7, 9-11, 17-21). Several retrospective analyses have suggested that doses higher than 60 Gy may improve local disease control and OS (5, 7, 19, 20). Schwegler *et al.* (21) carried out bronchoscopic biopsies after radiation and demonstrated the elimination of macro and microscopic tumor in 20.5% of patients after a dose of 60 Gy and 64% of patients after 80 Gy, with improved local relapse-free and OS with the higher dose. The radiation dose effect in stage III NSCLC is relatively limited (7, 22). In 72 patients with GTVs greater than 100 cc treated with radiation alone, Rengan *et al.* showed that radiation doses of 64 Gy and higher were associated with better survival than doses less than 64 Gy (median survival 20 months vs. 15 months, $P=0.068$) (7). Radiation dose was also an independent predictor of local failure-free survival with each 1 Gy increase in dose resulting in a 3.6% decreased risk of local failure. Machtay *et al.* performed a secondary analysis of 1,290 patients from six RTOG trials utilizing chemoradiation and reported a 1.8% decrease in the risk of death ($P<0.0001$) for every 1 Gy increase in BED. The odds ratio for local-regional failure was 0.77 for a 10 Gy increase in BED ($P<0.0001$) (22). The current analysis demonstrates that higher radiation doses were significantly associated with significantly improved OS in patients with stage III NSCLC treated with RT alone or with chemoradiation. For patients who received RT alone vs. chemoradiation, the hazard ratio was 0.973 vs. 0.979, respectively, per 1 Gy increase in BED ($P<0.001$). Thus, higher radiation doses may

improve OS not only for patients with stage III NSCLC treated with RT alone, but also for those treated with chemoradiation.

Although it has been established that the standard of care for locally advanced NSCLC is a combination of chemotherapy and radiation, the optimal strategy in terms of timing of chemotherapy and radiation continues to be investigated. There have been a few randomized studies which demonstrated that concurrent, as opposed to sequential, administration of chemotherapy and RT leads to a survival advantage (2, 3, 23, 24-26). The most common practice in the United States is concurrent chemoradiation (27). The supportive evidence of this practice, however, is not extensive. The phase II randomized LAMP trial showed that concurrent chemoradiation followed by adjuvant chemotherapy resulted in a median survival of 16.3 months compared to 13.0 months for sequential chemoradiation and 12.7 months for, induction chemotherapy followed by concurrent chemoradiation (23). The only phase III trial from the United States evaluating the timing of chemoradiotherapy is RTOG 9410, which has only been published in abstract form (3). This trial reported a median OS of 17 months in patients treated with concurrent chemotherapy with once daily radiation compared to 14.6 months in those treated with sequential chemoradiotherapy ($P=0.046$). In a large number of patients treated outside of a clinical trial, the current analysis confirms the superiority of concurrent chemoradiation over sequential chemoradiation.

The role of RT dose escalation in locally advanced NSCLC continues to be researched. Important questions remain to be answered about the potential benefits and risks of the use of higher RT doses in combination with concurrent chemotherapy. Similarly, the potential benefits of chemotherapy remain unclear in patients treated with higher doses of RT. In an attempt to address these issues, this analysis evaluated the product of BED and chemotherapy (BED*CHEMO) as a covariate in the Cox model to determine whether or not there was a significant interaction between RT dose and chemotherapy. The analysis showed no significant interaction between RT dose and chemotherapy suggesting that the impact of BED on survival did not vary with the use of chemotherapy. Thus, patients receiving chemotherapy may benefit from high dose RT and among those treated with high dose RT, chemotherapy may still be beneficial.

Many previous studies demonstrated that KPS and weight loss are significant factors affecting OS in patients with NSCLC (28, 29). The current study confirmed these findings with higher KPS ($P=0.020$) and weight loss $<5\%$ of total body weight ($P=0.017$) were being significantly correlated with improved OS. The current study, however, failed to show a significant prognostic effect for age, gender, smoking history, pre-RT oxygen use, or comorbidity score.

This analysis has limitations. It is a retrospective study which carries all of the weakness inherent in such an analysis. Considering the presence of many confounding factors, the number of cases was relatively small, so the study may be underpowered to detect relatively small differences in outcome. Because the range of radiation doses was rather narrow for all three groups of patients, the radiation dose effect should be interpreted with caution. The dose effect for patients treated with definitive intent of concurrent chemotherapy is not answered due to the relatively narrow dose-range given to these patients. Due to missing data points, no strong conclusions can be drawn regarding the overall effect of GTV. Non-uniform clinical conditions and the possible presence of other confounding factors, such as the inclusion of patients treated with palliative intent, may have obscured the effects of chemotherapy and RT on survival, though performance status and comorbidity scores were also considered during the analysis.

In summary, this analysis suggests that a higher radiation dose, the addition of chemotherapy and the use of concurrent chemoradiation are independent factors associated with improved OS in patients with stage III NSCLC. There was no interaction between the use of chemotherapy and the dose of radiation, suggesting the potential importance of both high-dose radiation and the use of chemotherapy. Future prospective studies are needed to establish optimal radiation doses both alone and in the setting of chemoradiation, RTOG 617 was recently activated to study the dose effect in patients with stage III NSCLC treated with concurrent chemoradiation.

Acknowledgments

This work was partially supported by the Pardee Foundation and Career Developmental Award from American Society of Clinical Oncology. We express our gratitude to all our patients. We also thank Brady T. West, the statistician lead of Center for Statistical Consultation and Research (CSCAR) for his assistance on statistical analysis.

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Figure 1A

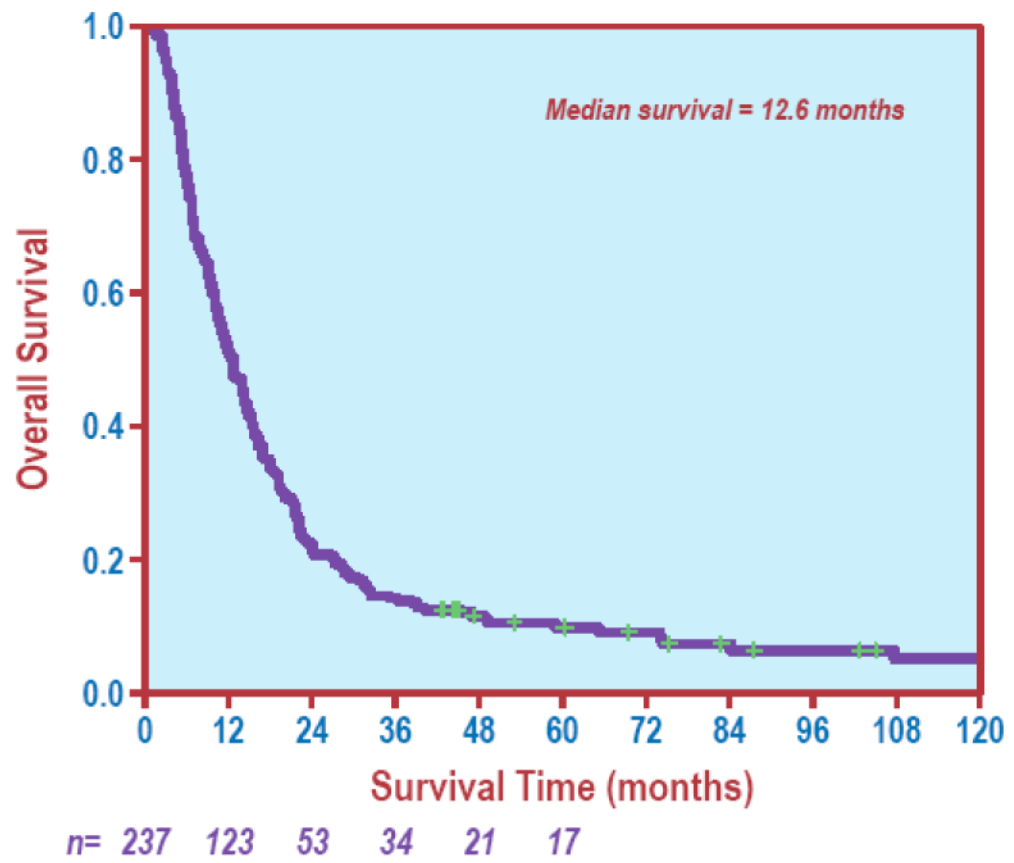
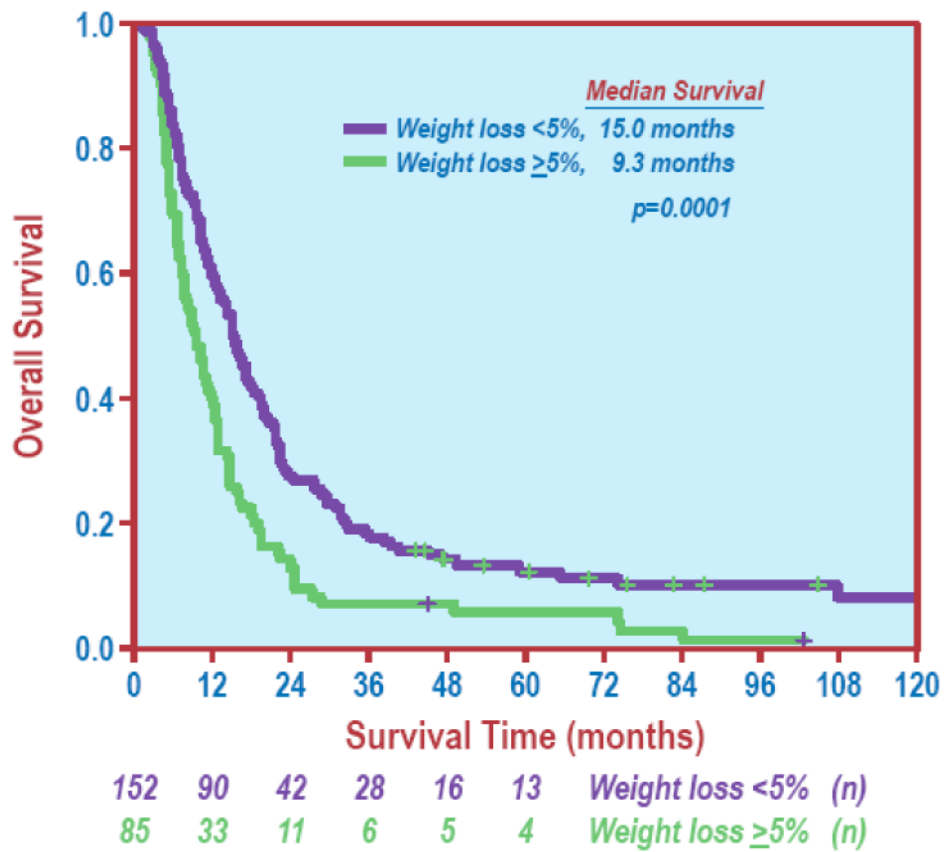


Figure 1B

**Figure 1.**

Overall survival. Figure 1A shows overall survival of the entire study group. Figure 1B depicts overall survival curves by weight loss (<5% vs. \geq 5%) with a significant difference in survival between the two groups (Log Rank test, $P=0.0001$).

Figure 2A

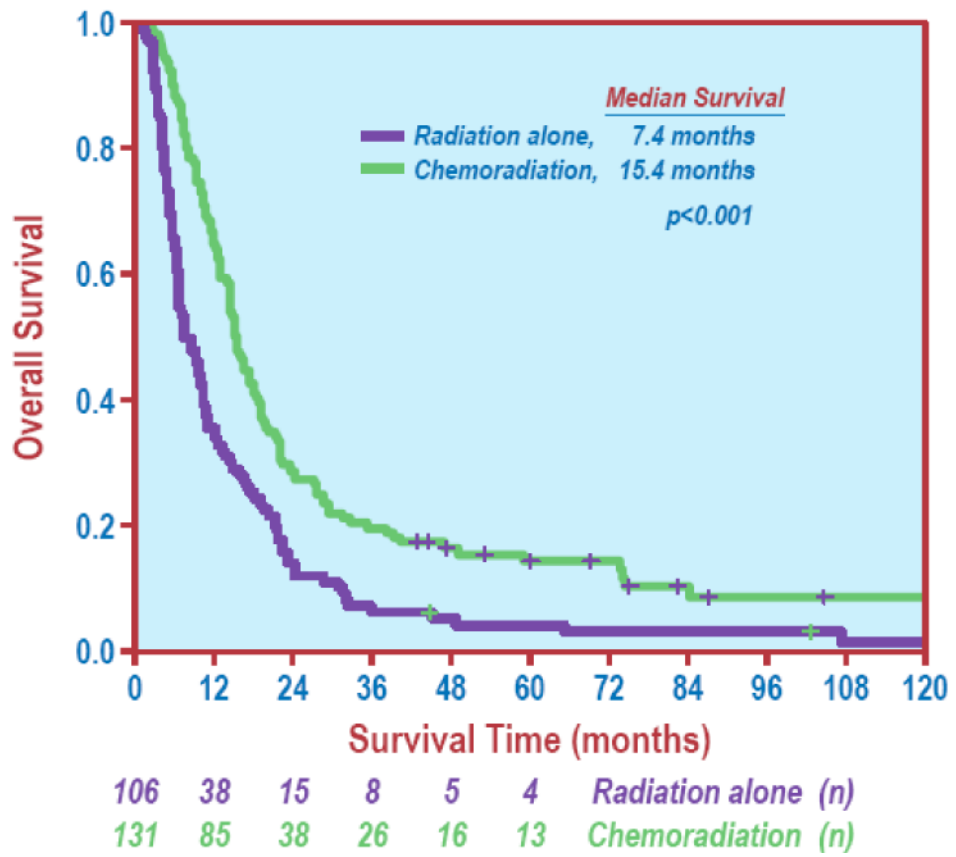
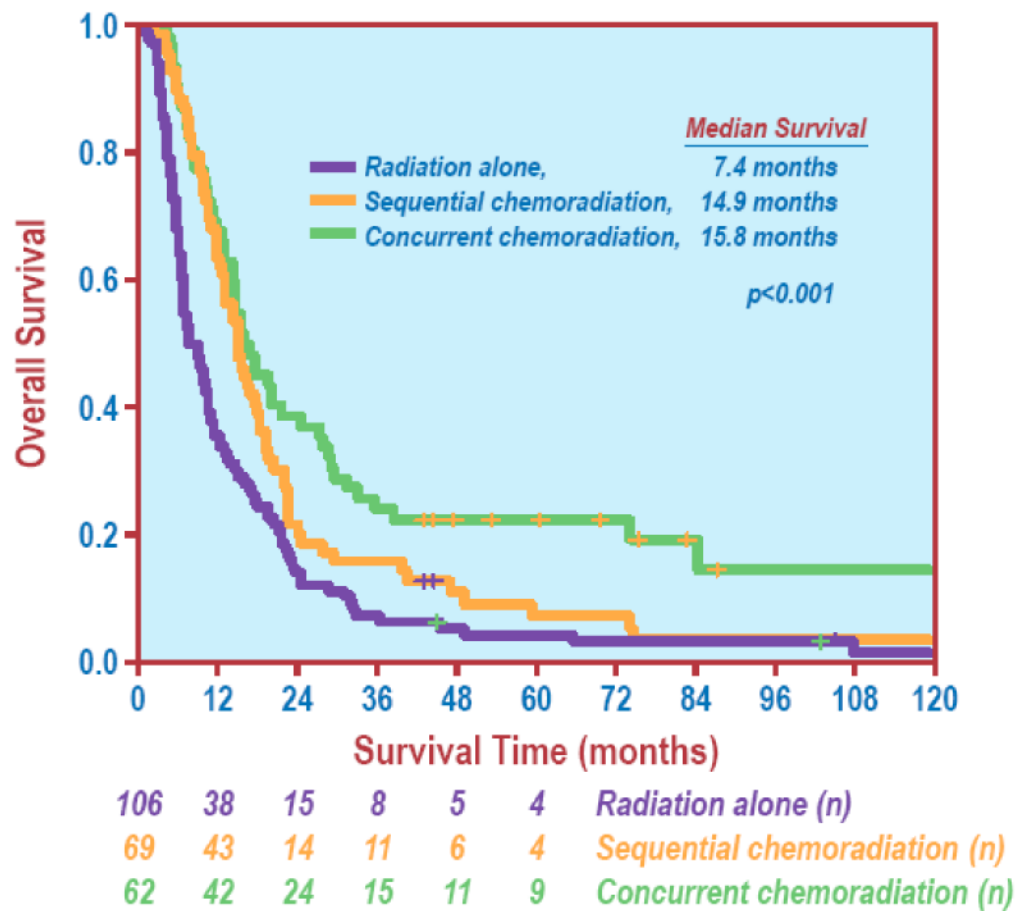


Figure 2B

**Figure 2.**

Chemotherapy and overall survival. Figure 2A demonstrates a significant difference in overall survival between radiation alone vs. chemoradiation (Log Rank test, $P < 0.001$). Figure 2B shows overall survival of patients treated with sequential chemoradiation or concurrent chemoradiation vs. radiation alone (Log Rank test, $P < 0.001$).

Figure 3A

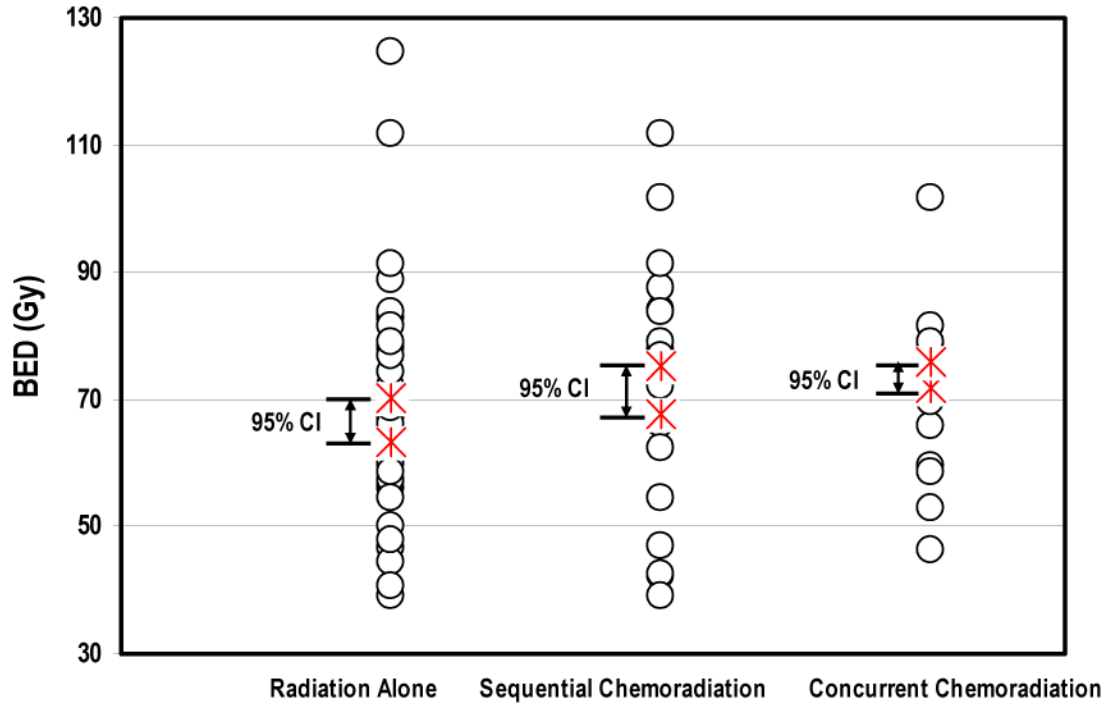


Figure 3B

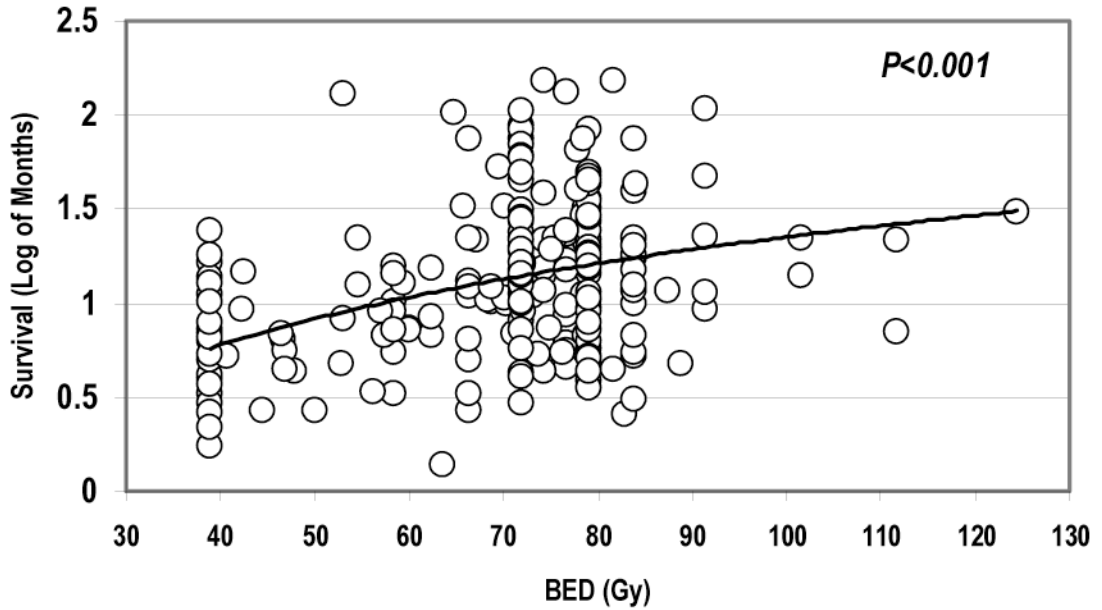


Figure 3. Radiation dose and overall survival. Figure 3A, showing the distribution of BED in patients treated with radiation alone, sequential chemoradiation, or concurrent chemoradiation. Figure 3B plots the relationship of survival over BED for all individual patients, showing that BED was a significant factor for overall survival (Cox-regression analysis, continuous covariate, $P < 0.001$).

Table 1
Patient, tumor and treatment characteristics and their effects on overall survival (univariate analysis)

Characteristic	No. of Patients	Median OS (months)	5 year OS	P value
Age	Median	65 years		
	Range	34 – 89 years		0.377 [‡]
Gender	34–65 years	121 (51.1%)	13.6	11.9%
	>65 years	116 (48.9%)	11.0	5.3%
	Male	170 (71.7%)	11.3	8.2%
	Female	67 (28.3%)	14.2	9.8%
KPS	Median	80		
	Range	60 – 100		0.029 [‡]
Weight loss 5%	< 80	11 (4.6%)	7.2	0.0%
	80	226 (95.4%)	12.8	10.4%
	Yes	85 (35.9%)	9.3	4.2%
	No	152 (64.1%)	15.0	11.3%
Smoking history	Yes	211 (89.0%)	12.2	8.9%
	No	26 (11.0%)	12.8	11.5%
Oxygen use pre-RT	Yes	19 (8.0%)	9.6	0.0%
	No	218 (92.0%)	12.8	10.1%
Comorbidity score	Median	2.0		
	Range	0-10		0.245 [‡]
Pleural effusion	0 - 2.0	152 (64.1%)	14.0	11.2%
	> 2	85 (35.9%)	10.8	5.7%
	Yes	52 (21.9%)	11.1	5.1%
Stage	No	185 (78.1%)	12.8	10.6%
	IIIA	102 (43.0%)	14.1	9.7%
	IIIB	135 (57.0%)	11.1	8.8%
Radiation dose escalation protocol	Yes	31 (13.1%)	15.6	6.5%
	No	206 (86.9%)	12.1	9.7%

Characteristic	No. of Patients	Median OS (months)	5 year OS	P value
Chemoradiation	Yes	131 (55.3%)	15.4	13.2% <0.001 [‡]
	No	106 (44.7%)	7.4	3.3%
BED	Median	72.2 Gy		
	Range	39 – 125 Gy		
		72	10.2	7.2% <0.001 [‡]
GTV [*]	> 72	118 (49.8%)	15.6	10.2% 0.018
	Median	187 cm ³		
	Range	1.6 – 1425 cm ³	16.4	7.4% 0.447 [‡]
	> 187 cm ³	50 (49.5%)	14.7	7.0% 0.619 [‡]

Abbreviations: KPS = Karnofsky performance score, RT = radiation therapy, BED = bioequivalent dose, GTV = gross tumor volume, OS = overall survival.

^{*} GTV data only available in 101 patients.

[‡] Log-rank test, categorical covariates or continuous covariate transform to categorical covariates by the median.

[‡] Cox-regression analysis, continuous covariate.

Table 2
Sequential and concurrent chemoradiation compared to radiation alone (multivariate analysis)

Factors	Estimated HR of death (95% CI)	P value*
KPS	0.964 (0.934 – 0.994)	0.020
Weight loss < 5%	0.702 (0.524 – 0.939)	0.017
Pre-RT oxygen use (yes vs. no)	1.393 (0.824 – 2.354)	0.215
Stage (IIIA vs. IIIB)	1.062 (0.799 – 1.413)	0.677
Concurrent CT-RT vs. RT alone	0.461 (0.322 – 0.662)	< 0.001
Sequential CT-RT vs. RT alone	0.692 (0.502 – 0.955)	0.025
BED (Gy)	0.976 (0.966 – 0.985)	< 0.001

Abbreviations: KPS = Karnofsky performance score, RT = radiation therapy, CT = chemotherapy, BED = bioequivalent dose, Gy = Gray, CI = confidence interval, HR = hazard ratio (risk of death).

* Multivariate Cox's proportional hazards model.

Table 3
Interaction between radiation dose and chemotherapy on overall survival, sequential and concurrent chemoradiation compared to radiation alone

Factors	Estimated HR of death (95% CI)	<i>P</i> value*
KPS	0.962 (0.933 – 0.993)	0.016
Weight loss < 5%	0.717 (0.535 – 0.963)	0.027
Pre-RT oxygen use (yes vs. no)	1.466 (0.861 – 2.497)	0.159
Stage (IIIA vs. IIIB)	1.079 (0.810 – 1.438)	0.603
Concurrent CT-RT vs. RT alone	0.180 (0.041 – 0.794)	0.024
Sequential CT-RT vs. RT alone	0.277 (0.065 – 1.175)	0.082
BED (Gy)	0.970 (0.957 – 0.983)	< 0.001
BED *CHEMO	1.013 (.993 – 1.034)	0.200

Abbreviations: KPS = Karnofsky performance score, RT = radiation therapy, CT = chemotherapy, BED = bioequivalent dose, Gy = Gray, CI = confidence interval, HR = hazard ratio (hazard of death).

* Multivariate Cox's proportional hazards model.