DO ELDERLY PATIENTS WITH LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER BENEFIT FROM COMBINED MODALITY THERAPY? A SECONDARY ANALYSIS OF RTOG 94-10

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Data Availability Statement

All data will be made available per the NCTN Data Archive rules. The link for the archive is: https://nctn-data-archive.nci.nih.gov/.

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Purpose

Until 1994, elderly patients enrolled on RTOG trials evaluating bi-modality therapy did not appear to benefit from increased therapeutic intensity compared to radiation (TRT) alone (Lung Cancer 29 (suppl 1): 104, 2000, A-340). To determine if this observation still pertains, we evaluated outcome in elderly vs. younger patients enrolled on RTOG 94-10, a phase III trial comparing concurrent chemotherapy (CHM) and thoracic radiotherapy (TRT) to standard sequential CHM and TRT.

Materials and Methods

Patients on the sequential arm (SEQ) received cisplatin (P) 100 mg/m^2 days 1 and 29, vinblastine 5 mg/m^2 Q wk X 5, followed by 60 Gy TRT starting day 50; Arm 2 used identical CHM with 60 Gy TRT starting day 1 (CON-QD). Arm 3 employed P 50 mg/m^2 days 1, 8, 29, and 36, and etoposide 50 mg orally twice daily X 10, weeks 1, 2, 5, and 6, and 69.6 Gy in 1.2 Gy BID fractions starting day 1 (CON-BID). We used age 70 as the cut point and compared demographics and outcome with respect to toxicity; treatment completion rates and survival in each age group: $<$70 years and $\geq$ 70 years.

Results

From 1994 to 1998, 610 pts were enrolled; 595 (83%) were analyzable. 104 (17%) were $\geq$70 yrs of age, compared to 488 under 70 years. Demographics were similar between age groups. Grade $\geq$3 neutropenia and maximum toxicity per patient were more pronounced in the elderly in each arm. The incidence of severe esophagitis in those receiving CON-QD and CON-BID was higher in the elderly (33% and 60%, respectively) vs. those $<$70 yrs (23% and 42%, respectively); but median survival (MST) in the elderly and five-year survival rates favored concurrent chemoradiation: 22.4 mos and 22% for CON-QD vs. 16.4 mos and 10% for CON-BID vs. 10.8 mos and 8% for SEQ (p=0.069), whereas the MSTs for those <70 were 15.5 vs. 16 vs. 15.7 mos, respectively. Long-term toxicities were equivalent between those <70 and ≥70 yrs.

Conclusions

Fit, elderly patients enrolled on RTOG 9410, in contrast to historic precedent, benefited from concurrent chemoradiation. CON-QD therapy appeared superior to CON-BID therapy with respect to survival and esophagitis rates. Short-term toxicities were acceptable, though more pronounced in the elderly.

Summary Table

RTOG 9410: Comparison by Age Groups

Study Arm	SEQ		CON-QD		CON-BID	
Age	< 70	≥ 70	< 70	≥ 70	< 70	≥ 70
Number	161	40	177	24	153	40
Male (%)	61	73	63	67	66	65
SQ Histo (%)	35	48	37	54	39	28
Grade ≥3 Neutropenia (%)	73	83	77	92	48	68
Grade ≥3 Nausea/Emesis (%)	14	15	20	29	27	20
Esophagitis G ≥3%	4	0	23	33	42	60
Max toxicity (tox) G ≥4%	57	68	63	75	38	55
Late toxicity G ≥3%	15	18	18	17	21	23
Median survival (MST) mos	15.7	10.8	15.5	22.4	16	16.4

INTRODUCTION

Optimal therapy for elderly patients with locally advanced non-small cell lung cancer (NSCLC) is unknown. A subanalysis of RTOG 8808, which demonstrated a superior outcome for patients receiving sequential chemoradiation, compared to standard daily radiation (RT) alone, showed that this benefit was confined to patients under the age of 60. Five year survival rate in the combined modality group in this cohort was 13%, compared to 5% for those receiving standard daily RT alone, and only 2% for those receiving hyperfractionated (HFx) XRT (1). This difference was statistically significant at a p value of 0.02. Among the 64 patients 70 years of age or older, there were no long-term survivors, and no apparent difference in median survival between the three groups (p=0.56): 13.1 mos. for RT alone, 10.9 mos. for sequential chemoradiation, 9.4 mos. for HFxRT (2).

This analysis spurred a more in depth, retrospective review of recent RTOG studies, evaluating outcome vis à vis the elderly, in "good prognosis" patients with locally advanced NSCLC. This analysis, which included RTOG 8808 as well as other studies, failed to reveal a survival benefit in the elderly who received more intensive therapy. Of 749 patients accrued to studies conducted by RTOG between 1988 and 1994 in predominantly "good prognosis" LA-NSCLC, only 115 patients (15%) were 70 years of age or older (3). With few exceptions, the majority of these patients at baseline had reasonably good Karnofsky performance status (KPS ≥ 70) and ≤ 5% weight loss in the three months prior to diagnosis. There was no evidence of pleural effusion or distant metastasis. Patients enrolled on these studies received no prior chemotherapy or radiation. Hematologic toxicities and grade 5 adverse events were confined strictly to patients receiving combined modality therapy. In addition, esophagitis was much more pronounced in patients receiving concurrent chemoradiation, compared to those receiving sequential therapy or RT alone. There were no grade 3 or 4 late toxicities in patients receiving standard RT. Treatment disruptions and inability to complete treatment were more common in the elderly receiving combined modality therapy (21% vs. 15%). Overall, three-year survival in those under 70 was 18%, compared to 11% in those ≥ 70; five-year survival rates were 10% and 3%, respectively ($p=0.007$). Elderly patients receiving standard RT had a median survival equivalent to those receiving more intensive therapy. In contrast to the younger patient population, patients above the age of 70 did not benefit from increased therapeutic intensity. It was our conclusion, based on these efforts, that phase III studies specifically targeting the elderly were indicated.

However, in the interim, RTOG 94-10, a prospective, randomized phase III trial, which included both elderly and younger patients, completed accrual (4, 5). The results, which have been presented at ASCO (2000) , and subsequently published in the JNCI in 2011, demonstrated a statistically significant improvement in median survival for concurrent single daily chemoradiation (CON-QD), compared to sequential therapy (SEQ). A more aggressive, more toxic, concurrent hyperfractionated approach (CON-BID) did not prove significantly superior to the standard sequential arm. The medial survivals for CON-QD, SEQ and CON-BID were 17.1 mos, 14.6 mos. and 15.6 mos., respectively ($p=0.038$) with 5 year survival rates of 16%, 10% and 13% respectively. Although late grade 4 and 5 toxicities were no different between the three treatment arms, early toxicities (particularly esophagitis) were more pronounced for the concurrent approaches (45% for CON-BID, 22% for CON-QD, and 4% for SEQ therapy) ($p=<0.01$). This study, at the time, was the largest ever mounted in locally advanced NSCLC (Table 1). This paper constitutes a secondary analysis of age-specific treatment outcome on

RTOG 9410, and it focuses particularly on results in the elderly, defined as patients 70 years of age and older (6).

MATERIALS AND METHODS

Eligibility for RTOG 94-10 stipulated KPS ≥ 70, ≤ 5% weight loss over the preceding three months, minimal age of 18, diagnosis of medically inoperable stage II or IIIA NSCLC, or unresectable, locally advanced stage IIIA/IIIB NSCLC; and the absence of distant metastasis or clinically accessible pleural effusion. Prior chemotherapy, or radiation to the thorax, precluded enrollment. Treatment also mandated adequate physiologic indices: ANC ≥ 1800 mL, platelets ≥ 100,000 mL, hemoglobin ≥ 9 mg/dl, serum creatinine ≤ 1.5 mg/dl and bilirubin ≤ 1.5 mg/dl.

Randomization

Patients were randomized to one of three treatment regimens:

- Arm A employed sequential chemotherapy and radiation. Patients received induction therapy consisting of cisplatin 100 mg/m^2 days 1 and 29, and vinblastine 5 mg/m^2 weekly X 5 starting day 1. On day 50, full dose RT (60 Gy/2 Gy/fraction X 30 fractions) was begun.
- Patients enrolled on Arm B received identical chemotherapy and radiation, both modalities initiated day 1.
- Arm C stipulated hyperfractionated RT: (69.6 Gy/1.2 Gy BID X 6 weeks) and concurrent cisplatin 50 mg/m^2 days 1, 8, 29, and 36, and etoposide 50 mg/m^2 days 1-5 and 29-33.

Statistical Methodology

Age 70 was the cut point: within each treatment arm, we compared those under 70 to those 70 years of age or older; and then within each age cohort, in the context of the entire study, we compared outcome by treatment arm. Baseline demographics, toxicities, treatment completion rates, and median survival times as well as one, two and five year survival rates were compared. In addition, we conducted an analysis of progression free survival. All p values were two-sided and assessed by log rank.

RESULTS

Baseline Demographics

Baseline demographics for each arm of the study segregated by age are summarized in Tables 2A, 2B and 2C. No major imbalances were observed, although a higher proportion of patients ≥ 70 years in the concurrent QD group had squamous cell histology (54%) compared to those under the age of 70 (37%).

Toxicities (Tables 2A-C)

Overall, toxicities were generally worse amongst the elderly. This trend was particularly pronounced in older patients receiving concurrent chemoradiation. Grade ≥ 3 neutropenia was observed in 73% of those under the age of 70 receiving sequential therapy, compared to 83% of those 70 years of age or older. The incidence in the concurrent QD group was 77% and 92%, respectively; and in the concurrent BID group 48% and 68%, respectively. There was little difference in the incidence of nausea and vomiting segregated by age groups. However, more esophagitis occurred in the elderly receiving concurrent chemoradiation: 33% grade ≥ 3 in those ≥ 70 years receiving concurrent QD vs. 23% in those under the age of 70; the incidence was 60% and 42%, respectively, in those receiving concurrent BID RT. Maximum toxicities, across each treatment arm, were more pronounced in the elderly. There was no differences in grade ≥ 3 late toxicity.

Freedom from Progression

Time to progression (Figure 1) in the elderly enrolled in each of the three treatment arms was not statistically significantly different (p=0.728), whereas in younger patients (Figure 2), there was a trend toward therapeutic advantage for patients receiving concurrent chemotherapy and hyperfractionated RT (p=0.084).

Treatment Completion Rates

Treatment completion rates were in the 90% range and were similar for both age cohorts receiving standard daily RT (Table 3). However, the radiation completion rate for the elderly receiving hyperfractionated RT and concurrent chemoradiation was only 69% compared to 87% for those under the age of 70 (p=0.009).

Cause of Death

Overall, the majority of those who died (82%) succumbed to the underlying cancer. Five per cent died of complications from protocol therapy, and 11% from other causes. In 1%, complications of subsequent treatment were responsible for their demise, and in 2%, the cause of death was unknown. Of 594 evaluable patients, 536 (90.2%) as of five-year follow-up are deceased.

Survival Analysis

For those receiving sequential therapy, median survival time in younger patients was 15.7 mos., but only 10.8 mos. in the elderly. The relative one, two-year, and five-year survival rates were 61%,33% and 11% for the younger patients, and 50%, 29% and 8% for older patients (log rankp=0.11). . For patients receiving concurrent daily RT and chemotherapy, median survival time was 15.5 mos. for the younger patients and 22.4 mos. for patients 70 years of age or older. The respective one, two-year, and five-year survival rates were 60%, 30%, and 15% for younger patients and 79%, 46% and 22% for older patients (log rank p=0.40). For patients receiving concurrent twice daily RT and chemotherapy, the median survival for younger patients was 16 mos. and for older patients 16.4 mos., with relative one,two-year, and five-year survival rates of 60%, 34% and 14% for younger patients and 72%, 28%, and 10% for older patients (p=0.25).

Among younger patients, there was absolutely no significant difference in median survival time, or one, two- or five-year year survival rates between the three treatment arms (p=0.25) (Figure 3). However, for older patients, there was a significant difference clearly favoring the concurrent once daily chemoradiation approach (log rank p=0.022). Median, one, two-year and five-year survival rates are delineated in Figure 4.

CONCLUSIONS/DISCUSSION

In contrast to previous RTOG efforts, the fit elderly with locally advanced NSCLC enrolled on RTOG 94-10 appeared to benefit from combined modality therapy. In particular, concurrent daily chemoradiation yielded the best median survival amongst the elderly ($p=0.022$) and may have helped generate the survival difference ultimately observed in this study. Surprisingly, there was little difference between the three treatment arms in younger patients; but a numerically stark, albeit non-significant, difference emerged in elderly patients receiving concurrent daily chemoradiation compared to those receiving sequential chemoradiation, with a doubling of median survival time. These observations contrast with those previously observed in RTOG 8808, and in other contemporaneous phase II studies employing chemoradiation.

Acute toxicity, particularly esophagitis, tended to be worse in the elderly. Radiation completion rates were similar for the Arms A and B regardless of age, but showed a significant decrement (69% vs. 87%) in the elderly receiving concurrent twice daily radiation and chemotherapy; this higher incidence of treatment infidelity was likely attributable to enhanced toxicity. In addition, there was a trend toward increased myelosuppression, which has also been observed in advanced disease trials using chemotherapy alone (7, 8). There was no difference in the incidence or severity of long-term toxicities.

The explanation for the improvement in time to progression and survival for elderly enrolled on RTOG 94-10, compared to previous RTOG combined modality efforts, is unclear. There are a number of potential theories:

(1) Chance alone might have been responsible, but serendipity is unlikely given the size of this trial and the number of elderly enrolled;

(2) Patient selection, with minor, subtle variations in performance status may have favored the elderly. Alternatively, the elderly enrolled on RTOG 9410 may have been relatively fitter with fewer co-morbidities compared to their younger counterparts. However, review of baseline demographics failed to reveal any significant differences between the elderly and younger patients.

(3) Improved learning curve with better toxicity management and improved pro-active patient support might have been responsible. In the 10 to 15 years leading up to the initiation of this trial, the treatment of locally advanced NSCLC had become more standardized. Both radiation oncologists and medical oncologists had developed an increasing comfort level with and acceptance of combined modality treatment, in particular concurrent chemoradiation, but the learning curve, in this regard, would apply equally to both younger and older patients.

In the final analysis, there is no obvious reason why the elderly on RTOG 9410 out-performed their peers enrolled on prior efforts or why the elderly receiving concurrent daily radiation and chemotherapy did so much better than their peers receiving sequential therapy. The bottom line, however, is clear. The fit elderly should not be excluded from combined modality trials in locally advanced NSCLC. In contrast to observations gleaned from our previous efforts, the elderly clearly benefit. But outstanding questions exist. We need to better understand the influence of co-morbidities on toxicity and survival, and we need to assess the benefits, if any, in the fastest growing segment of the population, those over the age of 80, who are woefully under-represented in clinical trials. Very little data for this group exist.

To this end in an analysis of 125 LA-NSCLC patients aged 70 or more treated between 1990 and 2010 with either radiotherapy alone or chemotherapy and radiation, a simplified co-morbidity score proved to be a distinct prognostic factor.9 Those with a SMC of > 10 had poorer survival and more severe pulmonary toxicities.

Since the completion of RTOG 9410 and including data generated by this trial, Auperin and colleagues in a meta-analysis confirmed that concurrent chemoradiation was superior to sequential chemotherapy and radiation with roughly a 5% increase in 3 to 5 year OS. This difference was statistically significant.[10] Benefit appeared to be independent of age, though those over 70 constituted < 10% of enrollees on these trials. It is taken for granted that older patients enrolled on these trials are unlikely to be representative of the overall elderly population diagnosed with LA-NSCLC, but this presumption has never been proven. Regardless, with the median age of lung cancer now exceeding 70 years in the US, we need to be more pro-active in enrolling elderly individuals with LA-NSCLC onto clinical trials.

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FIGURE LEGENDS

Figure #1: There was no significant difference in time to progression for the elderly across each of the treatment arms (*p*=0.728). The percentage free from progression at one and two years is shown in the grid on the right for the elderly enrolled on each of the treatment arms.

STD50: sequential chemotherapy and XRT

STD1: concurrent chemotherapy and once a day XRT

HFx: concurrent chemotherapy and twice a day XRT

FFP: freedom from progression

FIGURE LEGENDS

Figure #2: A trend toward improved time to progression was noted in young patients (< 70 yrs) enrolled on the arm employing hyperfractionated XRT and concurrent chemotherapy (*p*=0.084). Freedom from progression at one and two years is shown in the grid on the right.

STD50: sequential chemotherapy and XRT

STD1: concurrent chemotherapy and once a day XRT

HFx: concurrent chemotherapy and twice a day XRT

FFP: freedom from progression

FIGURE LEGENDS

Figure #3: There was no significant difference in survival for younger patients on each of the treatment arms (*p*=0.464). Median survival ranged from 15.5 to 16 mos and 2-year survival rates ranged from 33% to 37%.

STD50: sequential chemotherapy and XRT

STD1: concurrent chemotherapy and once a day XRT

HFx: concurrent chemotherapy and twice a day XRT

FFP: freedom from progression

OS: overall survival

FIGURE LEGENDS

Figure #4: There was an important survival trend favoring concurrent once daily XRT and chemotherapy in the elderly (*p*=0.069). MSTs for the elderly receiving STD1 therapy vs. STD50 were 22.4 and 10.4 mos, respectively; and the relative 2-year survival rates were 46% and 29%, respectively.

STD50: sequential chemotherapy and XRT

STD1: concurrent chemotherapy and once a day XRT

HFx: concurrent chemotherapy and twice a day XRT

FFP: freedom from progression

OS: overall survival

MST: median survival time

TABLE 1

RTOG 9410 Sequential vs. Concurrent
RT+CT in Stage III NSCLC

Therapy	No. Pts	Med.Surv	5 yr OS	Gr 4-5 Tox	
				Early	Late
Seq[*,†]	199	14.6	10%	30%	14%
Con[‡] QD[*]	199	17.1	16%	48%	15%
Con BID[§]	199	15.6	13%	62%	16%
		p=0.046		p<.01	p=NS

[*]cisplatin/vinblastine; 60 Gy

[†]Seq = sequential

[‡]Con = concurrent

[§]cisplatin/etoposide; 69.6 Gy (1.2 Gy BiD)

Table 2A

RTOG 9410
Demographic Comparison by Age Groups

Sequential Tx

AGE (yrs)	< 70	≥ 70
Number	161	40
Male (%)	61	73
KPS* 90-100 (%)	76	75
SQ† Histo (%)	35	48
Stage IIIB (%)	55	50
Caucasian (%)	84	88
Grade ≥ 3 ANC‡ (%)	73	83
Grade ≥ 3 N/V§ (%)	14	15
Max toxicity (%)	57	68
Esophagitis Gr‖ ≥ 3 (%)	4	0
Late toxicity Gr ≥ 3 (%)	15	19
MSTΨ (mo)	15.7	10.8

*KPS ~ Karnofsky performance status
†SQ ~ squamous
‡ANC ~ absolute neutrophil count
§N/V ~ nausea and vomiting
‖Gr ~ grade
ΨMST ~ median survival time

Table 2B

RTOG 9410

Demographic Comparison by Age Groups

CON-QD

AGE (yrs)	< 70	≥ 70
Number	176	24
Male (%)	63	67
KPS* 90-100 (%)	75	75
SQ† Histo (%)	37	54
Stage IIIB (%)	55	50
Caucasian (%)	89	83
Grade ≥ 3 ANC‡ (%)	77	92
Grade ≥ 3 N/V§ (%)	20	29
Max toxicity (%)	63	75
Esophagitis Gr‖ ≥ 3 (%)	23	33
Late toxicity Gr ≥ 3 (%)	17	17
MSTΨ (mo)	15.5	22.4

*KPS ~ Karnofsky performance status

†SQ ~ squamous

‡ANC ~ absolute neutrophil count

§N/V ~ nausea and vomiting

‖Gr ~ grade

ΨMST ~ median survival time

Table 2C

RTOG 9410

Demographic Comparison by Age Groups

CON-BID

AGE (yrs)	< 70	≥ 70
Number	151	39
Male (%)	34	35
KPS* 90-100 (%)	71	85
SQ† Histo (%)	39	28
Stage IIIB (%)	57	48
Caucasian (%)	86	88
Grade ≥ 3 ANC‡ (%)	48	68
Grade ≥ 3 N/V§ (%)	27	20
Max toxicity (%)	38	55
Esophagitis Gr‖ ≥ 3 (%)	42	60
Late toxicity Gr ≥ 3 (%)	21	23
MSTΨ (mo)	16	16.4

*KPS ~ Karnofsky performance status

†SQ ~ squamous

‡ANC ~ absolute neutrophil count

§N/V ~ nausea and vomiting

‖Gr ~ grade

ΨMST ~ median survival time

Table 3

Tx Completion Rates

	STD 50		STD 1		HFX	
Age (yrs)	<70	≥70	<70	≥70	<70	≥70*
N	152	35	172	23	150	39
RT Complete (%)	89	91	93	91	87	69*
No Protocol RT (%)	4.6	2.9	0	0	0	0

*$p<0.05$

- vs HFx <70 and
- vs all other categories

NOTE: Figures for this paper are in Powerpoint in file: Figures for RTOG 9410 paper