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Patterns of Failure According to Tumor Histology and Treatment Schedule in Patients with Locally Advanced Inoperable Non-Small Cell Lung Cancer: Secondary Analysis of NRG Oncology RTOG 9410

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Abstract

Background and Purpose: *This secondary analysis of RTOG 9410 compared three chemoradiation treatment strategies for inoperable stage II-III non-small cell lung cancer~~)~~ was done to clarify patterns of failure by treatment and histology.*

Methods and Materials: *577 patients were treated with either sequential cisplatin based chemotherapy followed by radiation 63 Gy ,50 days later [n=195] or one of two forms of concurrent cisplatin based chemo-radiation 63 Gy in once-daily fractions, [n=195], or 69.6 Gy in twice-daily fractions; [n=187]. Outcomes were time to progression and components of initial failure, i.e., in the primary tumor, in-field with out-of-field nodes, distant metastases, and their relative prevalence by treatment and histology.*

Results*: Overall progression rates were 75.9% in the sequential group, 72.8% in the once-daily concurrent group, and 65.2% in the twice-daily concurrent group (in all, 65.1% for squamous tumors vs. 75.4% for nonsquamous). Time to any progression including infield was significantly shorter by sequential compared by twice-daily therapy regardless of histology; time to infield progression also differed in squamous tumors (shorter ~~for~~ by once-daily compared by twice-daily) and nonsquamous tumors (sequential was shorter than concurrent groups. The most prevalent initial sites of failure were distant metastases outside the brain and primary tumor.*

Conclusions*: Concurrent therapy produced longer infield failures than sequential therapy; that infield recurrence in squamous was significantly prolonged by twice daily concurrent treatment. Once-daily concurrent therapy showed that more distant (non-brain) metastases from non squamous tumors suggest that histology should be considered in the choice of therapy for non-small cell lung cancer.*

Keywords: *locally advanced NSCLC; squamous lung cancer; non squamous lung cancer; sequential chemoradiation therapy, concurrent chemoradiation therapy; progression-free survival*

Highlights

Concurrent chemoradiotherapy prolonged infield failures compared to sequential chemotherapy followed radiotherapy in the locally advanced Non Small Cell Lung Cancer (LANSCLC).

Local recurrence was more common in squamous histology.

Infield recurrence was significantly prolonged by twice daily concurrent treatment.

By screening Brain imaging in this study, distant metastatic failures were more common outside of brain in non squamous histology group which suggests PET scan is indicated to screen among LANSCL study in future.

Future trials of LANSCLC require histological documentation as well as genetic mutation which will influence different treatment approaches.

Introduction

Although the primary endpoint of the prospective phase III Radiation Therapy Oncology Group (RTOG) 9410 trial to compare three combinations of chemotherapy and radiation therapy identifying the most effective treatment, calculating survival end points, and evaluating the safety of the proposed regimens for locally advanced inoperable non-small cell lung cancer (LANSCLC) [1], responsible stewardship requires additional analyses to identify patterns and timing of failure, and prevent their recurrence. Previous similar efforts have proved useful in addressing patterns of failure in NSCLC [2-5]. We undertook here timing and sites of failure analysis based on treatment schedule and tumor histology. We describe here our findings from that analysis, with the goal of identifying whether chemoradiation schedule should differ according to tumor histology.

Material and Methods

Details of RTOG 9410 were published previously [1]. Briefly, participating physicians screened patients for eligibility and obtained informed consent. Patients were stratified by disease stage and performance status to ensure balanced distribution of patients and then randomly assigned to one of three treatment groups as described below. Patients had histologically confirmed stage II, IIIA, or IIIB disease and had Karnofsky's performance scores (KPS) of 70-100. All cases were inoperable for medical or surgical reasons. At the outset, no patient had distant metastasis, and none had had prior chemotherapy or prior thoracic or neck radiotherapy [1]. Patients with malignancy ≥3 years prior were eligible if currently free of that disease. Safety and efficacy findings from this trial were reported previously [1].

The sequential-treatment group received cisplatin (100 mg/m^2 on days 1 and 29) and vinblastine (5 mg/m^2 per week) for 5 weeks with 63 Gy of thoracic radiotherapy (TRT) daily beginning on day 50. Patients given concurrent chemotherapy (cCT) with once-daily TRT received the same chemotherapy with 63 Gy of (TRT) beginning on day 1. Patients in the cCT with twice-daily TRT received cisplatin (50 mg/m^2 on days 1, 8, 29, and 36) and oral etoposide (50 mg twice daily on days 1, 2, 5, and 6) for 10 weeks with 69.6 Gy delivered as 1.2-Gy twice-daily fractions beginning on day 1. The TRT field size was reduced over the course of treatment as described in [1].

The maximum dose to the spinal cord was 48 Gy at any level, and sparing of all normal lung was urged. Interruptions in therapy were permitted for as long as 1 week for esophageal toxicity ≥grade 3, including weight loss requiring supplemental feedings or an inability to tolerate liquids. Longer interruptions were considered a protocol violation. Toxicity was scored according to the RTOG acute radiation criteria [1, 6].

Patients were evaluated at baseline (2–4 weeks before study entry), weekly during therapy, before administration of cisplatin, and after therapy ended. Acute esophagitis, pneumonitis, and hematologic toxicity were assessed weekly during treatment, and swallowing was assessed during radiotherapy. Other evaluations are described in the trial report [1]. Patients were seen 1 month after therapy cessation, every 3 months for 2 years, every 6 months for 3 years, and annually thereafter.

The objectives of this secondary analysis were to study timing and patterns of failure based on tumor histology and treatment group to identify weaknesses and strengths of the study interventions. Outcomes of interest were time to any progression, time to in-field progression, and time to out-of-field progression including distant metastases (brain and other). Per the original RTOG 9410 protocol, therapy failure included

evidence of (a) progression of the primary tumor, measured as a 25% increase or greater in the sum of the products of two diameters of each measurable lesion or the unquestioned appearance of a new lesion; (b) nodal progression (growth of existing nodes or the appearance of lesions in previously uninvolved nodes) within the radiotherapy field; (c) development of nodal disease outside the radiotherapy field; or (d) development of distant metastases. Measurable lesions were assessed by the longest diameter seen on physical examination, X-ray, CT scan, or ultrasonography and by a line perpendicular to that diameter. Tumor histology was classified according to the original RTOG 9410 pathology criteria as squamous (SQ) or Nonsquamous (NSQ) (which included adenocarcinoma and undifferentiated large cell carcinoma) [1].

Theory/calculation

We used cross-tabulation tables to test differences between pairs of treatment groups, using the chi-square test at a significance level of 0.05. Fisher's exact test was used whenever one or more of the four cells had fewer than 5 patients. When any overall test resulted in a statistically significant value, we used a Tukey-type multiple comparison test to compare pairs of proportions in that cross-tabulation table [7]. To estimate the failure rates for certain outcome measures, we used the cumulative incidence method [8], and we compared pairs of treatment groups using Gray's test [9].

Results

Patient Characteristics by Treatment Group

Complete information on patient characteristics was given in the trial report [1]. Briefly, of the 577 subjects evaluated, more than half were aged ≥60 years; men out numbered women by 1.8:1; and most (86.5%) were white. More than three-quarters of subjects had a KPS at or above 90. Most cases (56.5%) were staged as IIIB, followed by IIIA (41.6%) and II (1.9%). Overall, 232 cases (40.2%) were classed as SQ and 345 cases (59.8%) were classed as NSQ.

Patterns of Failure

The median follow-up time (MFUT) for all 577 patients was 1.3 years (range 0.4–17.0 years); MFUT for the 21 patients known to be alive at the time of analysis was 13.6 years (range 4.6–17.0 years); and MFUT time for 2 patients lost FU was 0.9 years (range 0.8–1.0 years). In each of the three study groups, 65% or more experienced disease progression: 148/195 (75.9%) of those given sequential therapy, 142/195 (72.8%) of those given concurrent therapy (cCT-TRT) with once-daily TRT, and 123/187 (65.8%) in those given cCT-TRT) with twice-daily radiotherapy. Among patients with SQ, 152/232 (65.5%) experienced disease progression at any site compared with 261 of the 345 (75.6%) with NSQ (statistically not significant).

Regarding to time to any failure, failure at any site had occurred in 45.5% or more in each group by year 1 and in as many as 73.8% at 5 years (Table 1, Fig. 1). Overall, more patients experienced failure at any site, at any time in the sequential group than in the concurrent twice-daily group (P=0.02, Gray's test). No significant differences in time to failure were found between treatment groups for patients with SQ (Fig. 1B), but for those with NSQ, more patients in the sequential group had failure at any time than in the concurrent twice-daily radiotherapy group (P=0.046, Gray's test) (Table 1, Fig. 1C).

Table 1.*Time to progression at any site by treatment group and histology*

	Sequential Chemoradiation		Concurrent Chemoradiation			
			Once-DailyXRT		Twice-DailyXRT	
	% with Failure No.at		% with Failure No.at		% with Failure No. at	
	(95%CI)	Risk	(95%CI)	Risk	(95%CI)	Risk
All Patients [a]						
Rate at 1 year	54.4(47.1,61.1)	64	46.7(39.5,53.5)	81	45.5(38.2,52.4)	67
Rate at 3 years	71.3(64.3,77.1)	22	65.6(58.5,71.9)	33	61.0(53.5,67.6)	26
Rate at 5 years	73.8(67.0,79.5)	13	69.7(62.7,75.7)	20	63.6(56.2,70.1)	15
No. with Failure/Total	148/195		142/195		123/187	

Patients with Squamous Tumors						
Rate at 1 year	49.4(37.6,60.0)	23	36.4(25.7,47.1)	33	42.3(31.1,53.0)	25
Rate at 3 years	66.2(54.2,75.8)	6	61.0(49.0,71.1)	11	53.8(42.0,64.3)	9
Rate at 5 years	66.2(54.2,75.8)	6	64.9(52.9,74.6)	5	57.7(45.7,68.0)	4
No. with Failure/Total	53/77		52/77		47/78	
Patients with Nonsquamous Tumors [b]						
Rate at 1 year	57.6(48.1,66.6)	41	53.4(43.9,62.0)	48	47.7(38.0,56.8)	42
Rate at 3 years	74.6(65.6,81.6)	16	68.6(59.3,76.3)	22	66.1(56.2,74.2)	17
Rate at 5 years	78.8(70.1,85.3)	7	72.9(63.8,80.1)	15	67.9(58.1,75.9)	11
No. with Failure/Total	95/118		90/118		76/109	

[a]Sequential vs. Concurrent–twice daily: $p = 0.02$ (Gray's test).

[b]Sequential vs. Concurrent–twice daily: $p = 0.046$ (Gray's test).

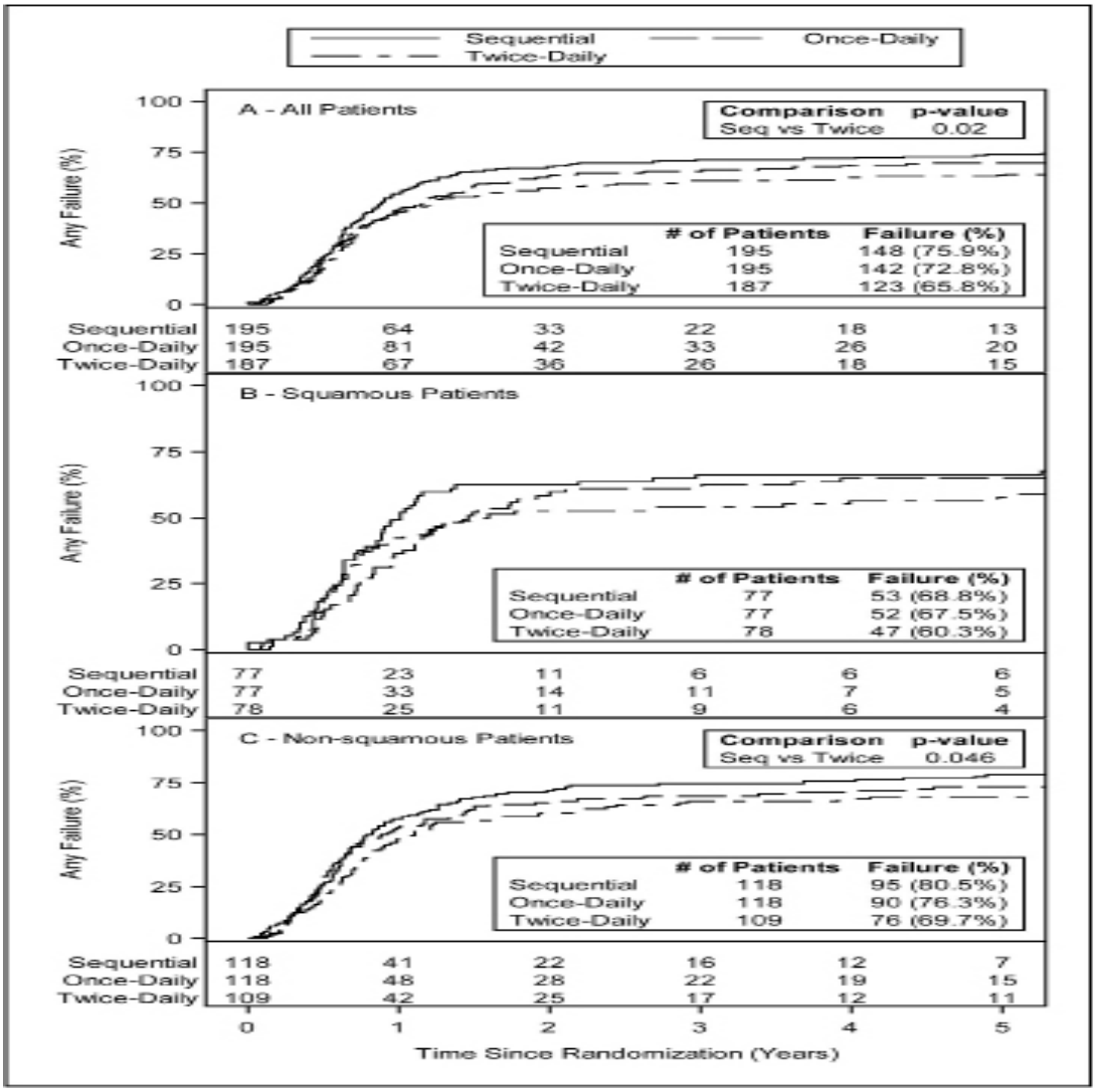

Fig 1. *Time to first failure at any site.* ***A,*** *all histologies;* ***B,*** *squamous histology;* ***C,*** *nonsquamous histology*

Regarding to in-field failure, between one-fifth and one-third of all patients experienced in-field failure during the first year after treatment (range, 20.9%–30.8%), and by the fifth year this range had risen to 36.6%–47.7% (Table 2, Fig, 2A). When this analysis was conducted, the time to in-field failure was again worse in the sequential group than in the cCT-TRT twice-daily group, both for all patients (*P*=0.01, Gray's test) and for those with NSQ (*P*=0.04, Gray's test); in the latter group, time to in-field failure was also significantly different between the sequential and concurrent once-daily group (*P*<0.01; Figs. 2B, C). Among patients with SQ, time to failure was almost significantly longer regarding infield failure in the twice-daily group than in the once-daily group (*P*=0.05; Fig. 3B).

Table 2. *Time to in-field progression by treatment group and histology*

	Sequential Chemoradiation		Concurrent Chemoradiation			
			Once-DailyXRT		Twice-DailyXRT	
	% with Failure No.at		% with Failure No.at		% with Failure No. at	
	(95%CI)	Risk	(95%CI)	Risk	(95%CI)	Risk
All Patients [a]						
Rate at 1 year	30.8 (24.4, 37.3)	81	22.1 (16.5, 28.1)	97	20.9 (15.4, 27.0)	92
Rate at 3 years	46.2 (39.0, 53.0)	27	37.6 (30.8, 44.4)	38	34.4 (27.6, 41.3)	35
Rate at 5 years	47.7 (40.5, 54.5)	14	39.7 (32.7, 46.5)	25	36.6 (29.7, 43.6)	19
No. with Failure/Total	96/195		81/195		71/187	
Patients with Squamous Tumors [b]						
Rate at 1 year	31.2 (21.1, 41.7)	28	20.8 (12.5, 30.5)	38	18.1 (10.4, 27.4)	36
Rate at 3 years	44.2 (32.7, 55.0)	9	46.8 (35.2, 57.5)	12	32.5 (22.2, 43.2)	10
Rate at 5 years	44.2 (32.7, 55.0)	7	50.6 (38.8, 61.3)	6	35.1 (24.5, 45.9)	5
No. with Failure/Total	34/77		41/77		29/78	
Patients with Nonsquamous Tumors [c,d]						
Rate at 1 year	30.5 (22.4, 39.0)	53	22.9 (15.7, 30.8)	59	22.9 (15.5, 31.2)	56
Rate at 3 years	47.5 (38.1, 56.2)	18	31.5 (23.3, 40.0)	26	35.8 (26.8, 44.8)	25
Rate at 5 years	50.0 (40.6, 58.7)	7	32.4 (24.0, 40.9)	19	37.6 (28.5, 46.7)	14
No. with Failure/Total	61/118		40/118		42/109	

[a]Sequential vs. Concurrent–twice daily: p = 0.01 (Gray's test).

[b] Concurrent-daily vs. Concurrent–twice daily: p = 0.054 (Gray's test; borderline).

[c] Sequential vs. Concurrent-daily: p < 0.01 (Gray's test).

[d] Sequential vs. Concurrent–twice daily: p = 0.04 (Gray's test).

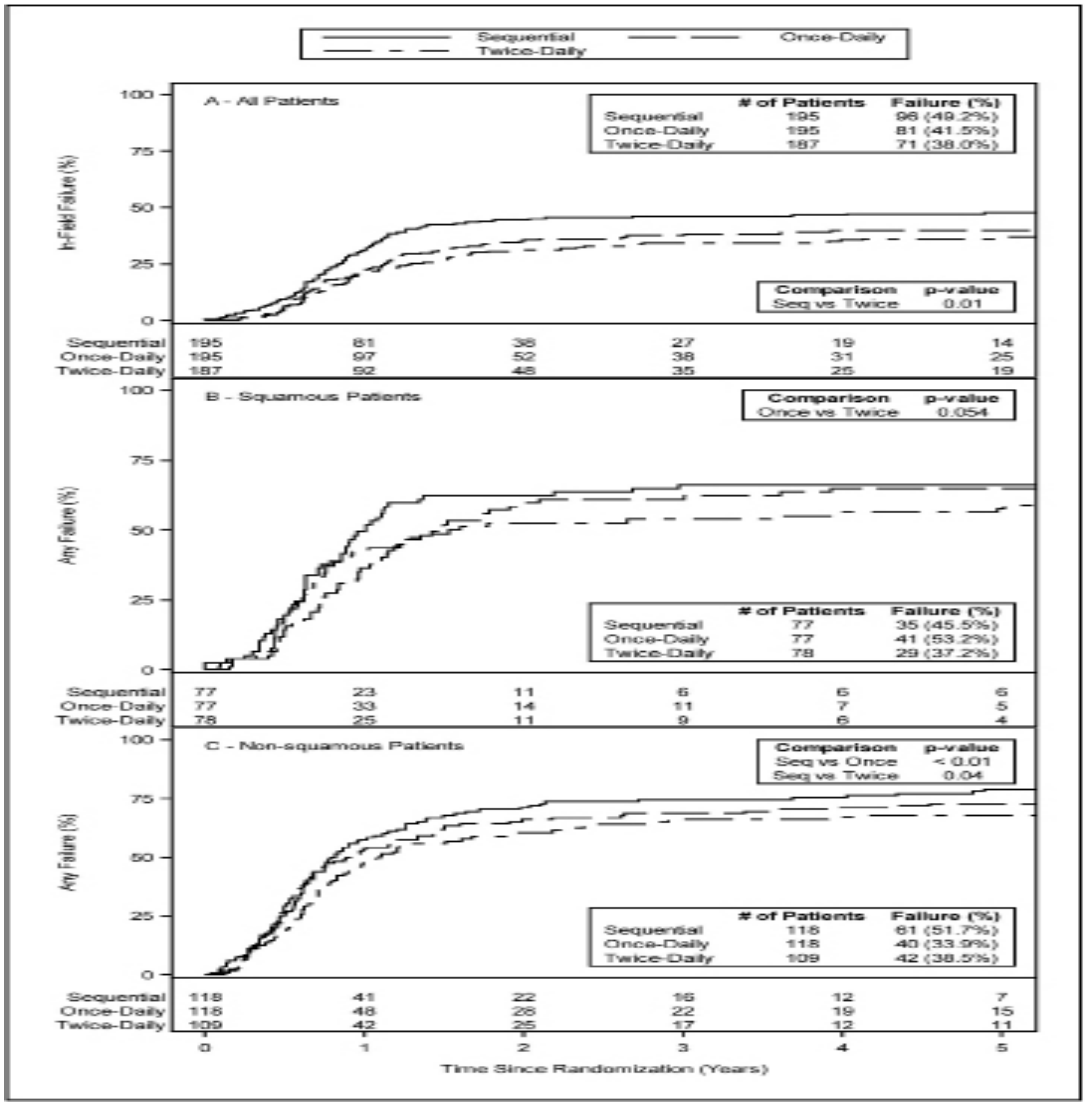

Fig 2. *Time to in-field failure.* ***A,*** *all histologies;* ***B,*** *squamous histology;* ***C,*** *nonsquamous histology.*

Sites of First Failure

First site failures are shown in Table 3. When all patients were considered together, more experienced failure exclusively outside the radiation treatment field (45%– 56%) than exclusively within it (31%–40%). Among patients with NSQ, first failure was more commonly out-of-field-only than in-field-only in all three treatment groups ,but no such pattern appeared for patients with SQ. Significant differences were found between treatment groups in terms of the proportions experiencing in-field-only first failures; specifically, for patients with SQ ,in-field-only failure was more common in the once-daily group (29 [56%]) than in the twice-daily group (17 [36%]) (*P*=0.02) (Table 3). For patients with NSQ, in-field-only failure was more common in the sequential group (36 [38%]) than in the once-daily group (20 [22%]) (*P*=0.03) (Table 3).

Finally, to determine if significant differences in component sites of first failure were present within each treatment group according to tumor histology, we divided each group according to SQ or NSQ histology. We found no significant differences in the patterns of failure according to histology in the sequential-therapy or cCT-TRT twice-daily group, but among those given cCT-TRT once-daily group, differences were found according to histology in four of the six components of failure, specifically patients with NSQ experienced fewer failures within the radiation field, and more distant failures, than did patients with SQ (Table 4).

Table 3. *Sites of first failure (in-field vs. out-of-field) by treatment group and histology*

	Sequential Chemoradiation	Concurrent Chemoradiation	
		Once-DailyXRT	Twice-DailyXRT
Site of First Failure	No. (%)	No.(%)	No.(%)
All Patients	*(n = 148)*	*(n = 142)*	*(n = 123)*
In-field only	59 (40)	49(35)	38(31)
Out-of-field only	67 (45)	73(51)	69(56)
Both in-field and out-of-field	22 (15)	20(14)	16(13)
Patients with Squamous Histology	*(n = 53)*	*(n = 52)* [a]	*(n = 47)* [a]
In-field only	**23 (43)**	**29 (56)**	**17 (36)**
Out-of-field only	22 (42)	13 (25)	25 (53)
Both in-field and out-of-field	8 (15)	10 (19)	5 (11)
Patients with Nonsquamous Histology	*(n = 95)* [b]	*(n = 90)* [b]	*(n = 76)*
In-field only	**36 (38)**	**20 (22)**	**21 (28)**
Out-of-field only	45 (47)	60 (67)	44 (58)
Both in-field and out-of-field	14 (15)	10 (11)	11 (15)

Note: Analysis is limited to patients with failure.

In-field is defined as primary (only), primary + nodes (in field), and nodes (in field) only.

Out of field is defined as nodes (out of field) only, nodes (out of field) + brain mets (metastases), nodes (out of field) + other mets, brain mets only, brain mets + other mets, and other mets only.

Both in-field and out-of-field is defined as all others, excluding in-field and out-of-field as defined above.

[a]Concurrent-daily versus Concurrent–twice daily: $P = 0.02$

[b]Sequential versus Concurrent-daily: $P = 0.03$

Table 4. *Component sites of first failure by histology for patients given concurrent chemotherapy with once-daily radiotherapy*

	Patients with Squamous Tumors	Patients with Nonsquamous Tumors	
Component Sites of First Failure	(n = 52) No. (%)	(n = 90) No. (%)	*P* Value
Primary tumor	30 (58)	26 (29)	< 0.01
Nodes	16 (31)	14 (16)	0.03
In field	16 (31)	8 (9)	< 0.01
Out of field	1 (2)	7 (8)	0.14
Brain	6 (12)	22 (24)	0.06
Other distant sites	17 (33)	47 (52)	0.02

Note: Patients may have more than one component site; therefore, percentages will not total 100%.

Discussion

Our key findings from this secondary analysis of failure patterns and timing were as follows. Sequential therapy was associated with less favorable outcomes than the once-daily or twice-daily cCT-TRT in nearly every comparison undertaken. Exceptions were in in-field–only and out-of-field–only initial failures, for which sequential therapy demonstrated significantly, better out-of-field–only control than did once-daily cCT-RT for patients with NSQ. Overall, patients in the once-daily cCT-TRT radiotherapy group had longer median survival times than did patients in the sequential therapy group [1]; however, overall measures of time to failure at any site or time to in-field failure indicated that twice-daily cCT-TRT produced significantly longer local control than did sequential therapy (Tables 1 and 2; Figs. 1 and 2). In both subgroups of patients (those with SQ and those with NSQ ,twice-daily cCT-TRT demonstrated significantly better control in measures of time to in-field progression relative to once-daily cCT-TRT (SQ) or sequential therapy (NSQ).

RTOG 9410 was one of a series undertaken by the RTOG to evaluate the efficacy and safety of cCT-TRT with standard and accelerated fractionation compared to sequential CT-TRT. Two groups, one with once-daily cCT-TRT and another with twice-daily cCT-TRT, were compared with a third in which the radiation therapy was given after chemotherapy. Overall, distant metastases outside the brain (first site of failure in 45%–49% of patients) and recurrence within primary tumors (first site of failure in 38%–44% of patients) proved the most difficult of disease components for these therapies to overcome. Other investigators have observed this pattern as well in studies of patients with stage IIIB NSCLC treated with combined radiotherapy and paclitaxel-and-cisplatin chemotherapy [10]. In our study, only for patients with SQ was cCT-TRT once-daily able to keep the initial failure rate from non-brain metastases to 33%, which is 10% lower than in either of the other two treatment groups' patients with SQ , and 19% lower than in patients with NSQ receiving the same treatment. Patients were also vulnerable to brain metastases, detected as an initial site of failure in 16%–20% overall, values roughly equivalent to the 19.9% population-based incidence of brain metastases in patients with lung cancer found in a regional study [11] and considerably higher than the 8.2% of patients with brain metastases found in Eastern Cooperative Oncology Group NSCLC trials since 1990 [12]. These statistics are meaningful because advanced NSCLC and metastasis are deadly: Five-year survival rates for patients with stage III NSCLC are about 10% [13], but this percentage declines to only 2.9% for patients with stage IV-NSCLC[14].

Overall, our analysis of initial failure sites revealed that none of the three treatments in this study demonstrated superior control of primary tumor; however, among patients with SQ, twice-daily cCT-TRT has produced significantly fewer initial failures in primary tumor than the once-daily cCT-TRT group (P=0.05). This is consistent with findings in two previous studies of hyperfractionation in which hyperfractionated TRT of 69.6 Gy with cisplatin based cCT–produced significantly greater in-field control (P=0.05) than did hyperfractionation alone [2] and lower rates of in-field failures (55%) compared with a combination of sequential therapy and cCT-TRT once daily (71%; P=0.015) [13]. In RTOG 9410, cCT-TRT twice-daily also led to significantly lower proportions of patients having in-field progression than did sequential therapy. In patients with SQ squamous t, cCT-TRT twice-daily led to overall fewer patients having in-field failures than did cCT-TRT once-daily, as well as smaller proportions of in-field-only and larger proportions of out-of-field-only as initial failures than did cCT-TRT once-daily. cCT-TRT Twice-daily also led to fewer initial failures in in-field nodes in patients with NSQ relative to sequential therapy. Finally, in both the SQ and NSQ subgroups, cCT-TRT twice-daily led to significantly longer times to in-field progression than did sequential therapy; for patients with SQ treated by cCT-TRT, twice-daily radiotherapy led to longer times to in-field progression than did once-daily treatment. Therefore, in both subgroups and overall comparisons, the twice-daily regimen demonstrated significantly better in-field control.

Although rates of first failures in brain or other distant sites were not statistically different among treatment groups, sequential treatment seemed to be associated with lower rates of brain and other distant metastases (DM)as first sites of failure (see "out-of-field only" on Table 3), both overall and in the NSQ subgroup. These apparently low rates of brain metastasis could be

related to the requirement that no evidence of brain metastasis by brain MRI or CT at staging. However, in the SQ subgroup, the cCT-TRT once-daily group had the fewest brain and other metastases among the treatment groups, although this apparent difference was not statistically significant and no three-way comparisons were done (Table 3). These findings are similar to the others [3], who found significantly lower rates of metastasis at sites other than brain in patients with SQ who underwent induction cisplatin and vinblastine chemotherapy with subsequent radiotherapy (16%) than in patients undergoing standard radiotherapy alone (43%) or hyperfractionated radiotherapy alone (38%) (P=0.0015). In the–current study, we found differences according to tumor histology in the once-daily radiotherapy group (Table 4), with the rate of brain metastases in the SQ group being half that in the NSQ group (12% vs. 24%; P=0.06) and about two thirds of that for metastases at sites other than brain (33% vs. 52%; P=0.02).

Just as the cCT-TRT twice-daily was able to control in-field among SQ group, the cCT-TRT once-daily regimen had in-field successes as well. Among patients with SQ treated by cCT-TRT once daily, produced the lowest proportion of out-of-field–only failure and, as mentioned previously, the lowest proportion of metastases in the brain and elsewhere. In comparison to sequential therapy, cCT-TRT once-daily led to significantly longer in- field failure times and significantly fewer in-field nodes as first failures. cCT-TRT-once-daily was also the only treatment that had different effects on initial failure sites according to histology, with primary tumor failure and in-field nodal failure being less common, and out-of-field failures more common, among patients with NSQ versus SQ (Table 4).

Outcomes for patients with lung cancer remain poor, especially for LANSCLC, which requires both more effective systemic therapy and optimized radiotherapy that considers dose-volume constraints for organs at risk [15, 16]. Patients with genetic mutations or other biomarkers may, with adequate analysis of biopsy samples and staging procedures, benefit from targeted therapy or immunotherapy [17, 18]. Patients whose tumors have no such markers may benefit from treatment that is chosen on the basis of tumor histology (SQ vs. NSQ) given the evident differences in patterns and timing of failure.

Medical oncologists have noted differences in patterns of failures and responses to according to the chemotherapeutic agents used. A prospective randomized study of various chemotherapy regimens for advanced NSCLC found overall survival to be significantly superior after cisplatin/pemetrexed versus cisplatin/gemcitabine for patients with adenocarcinoma or large-cell carcinoma; conversely, patients with SQ had better survival with cisplatin/gemcitabine versus cisplatin/pemetrexed [19].

Limitations of this analysis include its being based on data from a study that was not designed with stratification based on histology. Because this analysis was retrospective and the data were initially collected for other purposes, it is important to be conservative in drawing conclusions from this study's findings; indeed, our findings may most appropriately be considered hypothesis-generating. However, tumor histology (SQ vs. NSQ) was fairly well balanced in the three treatment groups. When this trial was conducted, the staging work-up involved CT scanning of the chest and upper abdomen and bone scans, but positron emission tomography (PET) was not required; thus patients were likely to have had occult distant (non-brain) metastases at staging. Treatment planning and delivery were done in 2 dimensions rather than the current 4-dimensional planning, and elective nodal irradiation was used. Image guidance was not used to contour the gross tumor volume, clinical target volume, or target volume, and no dose-volume constraints existed at the time. Also, treatment response was not assessed according to the Response Evaluation Criteria for Solid Tumors (RECIST) system [20], as that system had not been published when the trial was being designed. Nevertheless, RTOG 9410 was a prospective randomized study in which patients were assigned randomly, without bias, and all patients were treated similarly, and much of what was found has been verified in other studies. Our careful examination of patterns and timing of failure has revealed meaningful differences between treatment groups and between histologic types. These results can be used to plan effective therapy in clinical trials, to inform the design of additional studies, and to improve and standardize reporting of trials to improve comparability and to make treatment advances.

Conclusions

We found that DM was more common in NSQ histology, although sequential treatment group had less DM compared to cCT-TRT and local failure was more common in SQ histology as the first site of failure. cCT and accelerated twice daily TRT prolonged local failure compared to cCT and once daily TRT in SQ. Without PET scan as initial staging work-up, distant metastasis other than brain and primary failure were the most common sites of failure regardless histology and various combined chemoradiotherapy.

We need to give more selective treatment based on histology if patients do not have molecular or immunologically targeted LANSCLC.

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