TWICE-DAILY COMPARED WITH ONCE-DAILY THORACIC RADIOTHERAPY IN LIMITED SMALL-CELL LUNG CANCER TREATED CONCURRENTLY WITH CISPLATIN AND ETOPOSIDE

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ABSTRACT

Background For small-cell lung cancer confined to one hemithorax (limited small-cell lung cancer), thoracic radiotherapy improves survival, but the best ways of integrating chemotherapy and thoracic radiotherapy remain unsettled. Twice-daily accelerated thoracic radiotherapy has potential advantages over once-daily radiotherapy.

Methods We studied 417 patients with limited small-cell lung cancer. All the patients received four 21-day cycles of cisplatin plus etoposide. We randomly assigned these patients to receive a total of 45 Gy of concurrent thoracic radiotherapy, given either twice daily over a three-week period or once daily over a period of five weeks.

Results Twice-daily treatment beginning with the first cycle of chemotherapy significantly improved survival as compared with concurrent once-daily radiotherapy ($P=0.04$ by the log-rank test). After a median follow-up of almost 8 years, the median survival was 19 months for the once-daily group and 23 months for the twice-daily group. The survival rates for patients receiving once-daily radiotherapy were 41 percent at two years and 16 percent at five years. For patients receiving twice-daily radiotherapy, the survival rates were 47 percent at two years and 26 percent at five years. Grade 3 esophagitis was significantly more frequent with twice-daily thoracic radiotherapy, occurring in 27 percent of patients, as compared with 11 percent in the once-daily group ($P<0.001$).

Conclusions Four cycles of cisplatin plus etoposide and a course of radiotherapy (45 Gy, given either once or twice daily) beginning with cycle 1 of the chemotherapy resulted in overall two- and five-year survival rates of 44 percent and 23 percent, a considerable improvement in survival rates over previous results in patients with limited small-cell lung cancer. (N Engl J Med 1999;340:265-71.)

OF the approximately 170,000 cases of lung cancer diagnosed each year in the United States, 20 percent are small-cell cancers.[1] Staging systems divide small-cell lung cancer into two categories: limited and extensive. The former is clinically confined to one side of the chest and is treatable by radiotherapy field sizes (portals) tolerated by normal tissues.

The main treatment for limited small-cell lung cancer is radiotherapy and chemotherapy. Cisplatin plus etoposide has largely supplanted the older regimens of cyclophosphamide, doxorubicin, and vincristine. Advantages of the cisplatin–etoposide regimen over the older regimen include the absence of toxic effects on intrathoracic organs and the ability to use thoracic radiotherapy concurrently.

A meta-analysis of trials comparing chemotherapy alone with combined chemotherapy and thoracic radiotherapy found that combined treatment improved survival among patients with limited small-cell lung cancer,[2] but the best method of integrating thoracic radiotherapy with chemotherapy remained undefined. The optimal total dose, volume, duration, and timing of thoracic radiotherapy have not been tested in prospective trials. Fractionation of the customary once-daily radiotherapy dose into two treatments each day has biologic advantages and has been successful in pilot studies. In vitro, small-cell lung-cancer cell lines have marked radiosensitivity even to small doses of radiation.[3] The dose–response curves for small-cell lung-cancer cell lines lack a shoulder, which means that even at relatively low doses per fraction, small cells are killed exponentially; by contrast, radiation spares cell populations that have a shoulder. For these reasons, multiple small fractions of radiotherapy can kill small-cell cancer while reducing permanent damage to normal tissues. In addition, the use of small fractions may diminish the risks of late effects of radiation.

Pilot studies of twice-daily thoracic radiotherapy suggested that this therapy might have excellent results when combined with cisplatin and etoposide. The two-year survival rate was approximately 40 percent, and the rates of myelosuppression and esophagitis were tolerable: grade 3 granulocytopenia occurred in 70 to 80 percent of the treated patients and grade 3 esophagitis in 35 to 40 percent.[4-7]

Cisplatin–etoposide combined with once-daily radiotherapy was also examined in pilot studies.[8,9] The Southwest Oncology Group, using daily fractionated

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thoracic radiotherapy at a total dose of 45 Gy, reported a two-year survival rate of 40 percent.[9] Toxic effects were equally reversible in pilot studies of twice-daily or once-daily thoracic radiotherapy.

In this study of limited small-cell lung cancer, we compared once-daily and twice-daily thoracic radiotherapy while holding other variables constant.

METHODS

Patients

We enrolled 419 patients in the study, which began in May 1989 and ended in July 1992. Two patients were found to have been enrolled twice. The primary analysis thus included 417 patients and was conducted on an intention-to-treat basis. Of the 417 patients, 36 (21 receiving once-daily radiation and 15 receiving twice-daily radiation) were excluded from the analysis of eligible patients: 7 withdrew from treatment and never received any therapy according to the protocol, and 29 were found to be ineligible. The reasons for ineligibility were the absence of pretreatment tumor measurements (eight patients), extensive disease (six), histologic findings of non–small-cell cancer (six), incomplete staging studies (five), elevated serum aspartate aminotransferase level (one), incorrect diagnosis (one), inadequate performance status[10] (see below; one), and absence of on-study data (one). Thus, 381 patients (185 receiving once-daily treatment and 196 receiving twice-daily treatment) were eligible for a secondary analysis.

For patients to be eligible the small-cell lung cancer had to be confined to one hemithorax, the ipsilateral supraclavicular fossa, or both. Patients with pleural effusions found on chest films were excluded, regardless of cytologic findings, as were patients with contralateral hilar or supraclavicular adenopathy. Staging was done by computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and brain; radionuclide bone scanning; and bilateral iliac-crest bone marrow aspiration and biopsy. Adequate organ function was defined as a white-cell count of at least 4000 per cubic millimeter, a platelet count of at least 100,000 per cubic millimeter, a serum creatinine level of less than 1.5 mg per deciliter (130 μmol per liter), serum aspartate aminotransferase and alanine aminotransferase levels less than two times the upper limit of normal, a serum bilirubin level of less than 0.5 mg per deciliter (8.6 μmol per liter), and a forced expiratory volume in one second of at least 1.0 liter. Symptomatic cardiac disease or a myocardial infarction within the previous six months was cause for exclusion. Patients had to be available for follow-up. In all cases, histologic or cytologic findings confirmed the diagnosis of small-cell lung cancer. Patients with prior cancer or prior treatment with either chemotherapy or radiotherapy were ineligible. All patients enrolled in the study gave informed consent.

Chemotherapy

The patients received four cycles of chemotherapy. Each three-week cycle consisted of 60 mg of cisplatin per square meter of body-surface area on day 1 and 120 mg of etoposide per square meter on days 1, 2, and 3. No dose adjustments were permitted for the first two cycles. During cycles 3 and 4, the dose of etoposide was reduced for patients with grade 4 toxic effects, febrile neutropenia or documented infection, or thrombocytopenia associated with bleeding. The dose of cisplatin was reduced during cycles 3 and 4 for patients with serum creatinine levels of 1.6 to 2.5 mg per deciliter (140 to 220 μmol per liter) and was further reduced if the levels were 2.6 mg per deciliter (230 μmol per liter) or higher.

Thoracic Radiotherapy

In both groups, the total dose of thoracic radiotherapy was 45 Gy for each patient. Patients receiving once-daily therapy received 1.8 Gy daily in 25 treatments over a period of five weeks. Accelerated twice-daily thoracic radiotherapy involved the administration of 1.5 Gy in 30 treatments over a period of three weeks. In both groups, thoracic radiotherapy began concurrently with the first cycle of chemotherapy.

The target volume for thoracic radiotherapy, which was similar in both groups, included the gross tumor, as defined by the chest CT scan, and the bilateral mediastinal and ipsilateral hilar lymph nodes. Irradiation of uninvolved supraclavicular fossae was forbidden. The inferior border extended 5 cm below the carina or to a level including ipsilateral hilar structures, whichever was lower. The clinically determined volume was expanded by a margin of 1 to 1.5 cm.

Radiotherapy treatment used linear accelerators; no cobalt-60 machines were allowed. Patients underwent treatment setup with radiotherapy simulators to mark field borders before treatment. Reduction of the field to conform to a smaller target volume after treatment was not allowed.

Interruptions of thoracic radiotherapy were discouraged, but it was interrupted when patients had platelet counts under 50,000 per cubic millimeter, weight loss of 4.5 kg (10 lb) or more (grade 2), or hospitalization for neutropenic fever or sepsis, but not when patients had difficulty swallowing or fever with low white-cell counts.

Prophylactic Cranial Irradiation

Systemic therapy was scheduled to last 12 weeks. The stage of disease was then determined again according to the results of chest radiography and head and chest CT. Because of the high frequency of brain metastases (50 percent), patients with a complete response were offered prophylactic cranial irradiation, despite reports of neurotoxicity.[11] This treatment consisted of 10 doses of 2.5 Gy to the midplane of the brain over a two-week period, for a total of 25 Gy.[12]

Measurement of Response

A complete response was defined as the disappearance of all clinical evidence of tumor. A decrease of 50 percent or more in the product of the length and width of any measurable tumor for at least four weeks was counted as a partial response. The disease was considered to have progressed if the patient lost more than 10 percent of body weight, if there was a 25 percent increase in the diameter of any tumor 2.0 cm or more in diameter or a 50 percent increase in the diameter of any tumor less than 2.0 cm in diameter, or if any new tumor appeared.

End Points

Overall survival, the primary end point of the trial, was measured from the date of entry into the study to the date of death from any cause. Treatment was considered to have failed if there was objective evidence of disease progression, regardless of tumor response, or death without clear-cut evidence of tumor progression. Failure was considered local when an intrathoracic relapse occurred after a complete response or when there was no complete response.

Statistical Analysis

The target enrollment was 400 patients. This sample size would give the study an 82 percent power to detect an absolute difference in two-year survival rates of 15 percent (25 percent for patients receiving once-daily treatment and 40 percent for patients receiving twice-daily treatment) at the 0.05 level with a two-sided test. This difference is equivalent to a 50 percent increase in median survival under the assumption of exponential distribution of survival.

With the exponential distribution of survival, we expected to detect a hazard ratio of 1.4 after adjustment for variations in radiotherapy and a total of 353 deaths by the end of the study.

Patients were randomized according to a permuted-block scheme, stratified according to Eastern Cooperative Oncology Group performance status (0 or 1 vs. 2), sex, and weight loss during the six months before entry (less than 5 percent of body weight vs. 5 percent or more).[13]

The survival distributions for overall survival and time to treatment failure were estimated according to the method of Kaplan

and Meier.[14] For comparison of ordinal data, such as the incidence of toxic effects, an exact Kruskal–Wallis test was used.[15] For comparison of binary data, such as response rates, Fisher's exact test was used.[16] For comparison of the survival distributions, a Mantel log-rank test was used for discrete covariates,[17] with stratification according to the stratification variables unless otherwise indicated. All P values are based on two-sided tests.

In our analysis of prognostic factors, the proportional-hazards regression model was used to estimate the joint effect of prognostic factors on survival.[18] A step-down procedure that consisted of dropping the least significant covariates, one at a time, was used to obtain a more parsimonious model.

RESULTS

Table 1 shows the main characteristics of the 417 patients, of whom 206 received once-daily therapy and 211 twice-daily therapy. The median age was 63 years (range, 34 to 80) for the patients receiving once-daily therapy, and 61 years (range, 30 to 82) for the patients receiving twice-daily therapy. Forty percent of the patients assigned to once-daily therapy were over 65 years of age, as compared with 31 percent of those assigned to twice-daily therapy (P= 0.07). All other variables were well balanced. Only 8 (2 percent) of the 356 patients for whom histologic data were available had variant histologic findings, an admixture of large-cell and small-cell lung cancer thought to be associated with a poorer prognosis.[3]

Toxic Effects

Tables 2 and 3 show the toxic effects observed among 409 patients, including 28 ineligible patients. Despite major myelosuppression (in approxi-

TABLE 1. CHARACTERISTICS OF THE STUDY PATIENTS ACCORDING TO ASSIGNED TREATMENT.

CHARACTERISTIC	ONCE-DAILY RADIOTHERAPY (N=206)	TWICE-DAILY RADIOTHERAPY (N=211)	P VALUE
Age			0.07
Median (yr)	63	61	
Range (yr)	34–80	30–82	
≤65 yr (%)	60	69	
>65 yr (%)	40	31	
Sex (%)			0.84
Male	59	58	
Female	41	42	
Race (%)			0.97
White	90	89	
Black	7	8	
Other	3	3	
Performance status (%)			0.48
0	43	39	
1	51	55	
2	5	5	
Weight loss (%)			0.93
None	54	57	
<5%	26	24	
5–10%	15	13	
>10%	5	5	
Morphologic features (%)*			1.00
Classic	98	98	
Variant	2	2	
Disease site (%)†			
Ipsilateral lung	49	55	0.24
Mediastinum	59	62	0.62
Ipsilateral supraclavicular fossa nodes	3	5	0.47

*Data on morphology were available for 175 patients receiving once-daily radiotherapy and 181 patients receiving twice-daily radiotherapy.

†Patients could have disease in more than one site.

TABLE 2. TREATMENT COMPLICATIONS ACCORDING TO THE FREQUENCY OF RADIOTHERAPY.*

COMPLICATION AND NO. OF RADIATION TREATMENTS PER DAY	GRADE						P VALUE
	0	1	2	3	4	5	
	number (percent) of patients						
Overall†							0.80
1	1 (0.5)	3 (1)	20 (10)	47 (23)	127 (63)	5 (2)	
2	2 (1)	0	19 (9)	51 (25)	128 (62)	6 (3)	
Myelotoxicity‡							0.70
1	2 (1)	9 (4)	19 (9)	43 (21)	129 (64)	1 (0.5)	
2	7 (3)	2 (1)	18 (9)	52 (25)	127 (62)	0	
Esophagitis							<0.001
1	113 (56)	19 (9)	38 (19)	22 (11)	11 (5)	0	
2	76 (37)	26 (13)	37 (18)	56 (27)	11 (5)	0	
Other toxic effects							0.20
1	4 (2)	18 (9)	119 (59)	46 (23)	12 (6)	4 (2)	
2	2 (1)	13 (6)	119 (58)	53 (26)	13 (6)	6 (3)	

*Data were available for 203 patients receiving once-daily radiotherapy and 206 patients receiving twice-daily therapy.

†Overall rates are based on the grade of the most severe complication of any type that occurred in each patient.

‡Myelotoxicity was defined as any decrease in marrow-derived cells in the peripheral-blood counts.[10]

TABLE 3. INCIDENCE OF TOXIC EFFECTS ACCORDING TO THE FREQUENCY OF RADIOTHERAPY.*

TOXIC EFFECT AND NO. OF RADIATION TREATMENTS PER DAY	GRADE					P VALUE
	1	2	3	4	5	
	number (percent) of patients					
Hematologic effects						
Leukopenia†						0.35
1	11 (5)	25 (12)	84 (41)	79 (39)	0	
2	2 (1)	26 (13)	79 (38)	90 (44)	0	
Granulocytopenia‡						0.75
1	11 (5)	15 (7)	31 (15)	122 (60)	0	
2	4 (2)	16 (8)	44 (21)	122 (59)	0	
Thrombocytopenia						0.83
1	47 (23)	30 (15)	32 (16)	16 (8)	0	
2	68 (33)	23 (11)	27 (13)	16 (8)	0	
Anemia						0.93
1	32 (16)	87 (43)	46 (23)	6 (3)	0	
2	38 (18)	79 (38)	47 (23)	10 (5)	0	
Infection						0.10
1	3 (1)	22 (11)	12 (6)	2 (1)	2 (1)	
2	5 (2)	34 (16)	12 (6)	4 (2)	2 (1)	
Fever						0.25
1	33 (16)	44 (22)	0	0	0	
2	47 (23)	46 (22)	0	0	0	
Vomiting						0.11
1	58 (29)	63 (31)	16 (8)	5 (2)	0	
2	50 (24)	55 (27)	17 (8)	3 (1)	0	
Pulmonary effects						0.97
1	18 (9)	13 (6)	6 (3)	1 (0.5)	1 (0.5)	
2	10 (5)	14 (7)	9 (4)	2 (1)	3 (1)	
Weight loss						0.05
1	65 (32)	47 (23)	6 (3)	0	0	
2	63 (30)	69 (33)	4 (2)	0	0	

*Data were available for 203 patients receiving once-daily radiotherapy and 206 patients receiving twice-daily therapy. A grade of 0 (data not shown) was given in the absence of a toxic effect.

†Leukopenia was defined as a decrease in the white-cell count.[10]

‡Granulocytopenia was defined as a decrease in polymorphonuclear neutrophils (granulocytes).[10]

TABLE 4. RESULTS ACCORDING TO THE FREQUENCY OF RADIOTHERAPY.

RESULT	ONCE-DAILY RADIOTHERAPY (N=185)	TWICE-DAILY RADIOTHERAPY (N=196)	P VALUE
	percent		
Response			0.23
Complete	49	56	
Partial	38	31	
Total	87	87	
No change	4	4	
Progressive disease	8	6	
Could not be evaluated	2	4	

mately 90 percent of patients in both groups), there was only one death from myelotoxicity. Overall, there were only 11 treatment-related deaths (6 in the group receiving twice-daily therapy and 5 in the group receiving once-daily therapy). No hematopoietic growth factors were used.

There were significant differences between the groups in the incidence of esophagitis ($P<0.001$). Fifty-six percent of the patients receiving once-daily therapy and 37 percent of those receiving twice-daily therapy had no esophageal toxic effects (grade 0). Grade 3 toxicity, defined as an inability to swallow solids, requiring narcotic analgesics or the use of a feeding tube, occurred in 11 percent of patients receiving once-daily therapy and 27 percent of those receiving twice-daily therapy. There was no difference between the groups in the incidence of grade 4 toxicity (hospitalization of the patient or perforation of the esophagus). There were no reports of permanent stricture due to the acute esophagitis. The duration of esophagitis was not a study end point.

Response Rates

Table 4 shows the response rates of the 381 eligible patients. Nearly 90 percent had objective responses. There was no significant difference in the response rate between the groups, nor did the rate differ significantly between the eight patients with variant histologic findings and the patients with standard histologic findings.

Survival

As of this writing, the median follow-up was almost eight years, and the minimal potential follow-up was approaching five years. Of the 417 patients, 335 had died: 175 patients who received once-daily therapy (85 percent) and 160 patients who received twice-daily therapy (76 percent). The median survival was 20 months for all patients, 19 months for those receiving once-daily therapy, and 23 months for those receiving twice-daily therapy. The two-year survival rate was 44 percent for all patients, 41 percent for those receiving once-daily therapy, and 47 percent for those receiving twice-daily therapy (standard error for both groups, 3 percent). The five-year survival rate was 23 percent for all patients, 16 percent for those receiving once-daily therapy, and 26 percent for those receiving twice-daily therapy (standard error for both groups, 3 percent). The difference in survival between the two groups was statistically significant ($P=0.04$ by the log-rank test). The estimated hazard ratio for death with once-daily treatment as compared with twice-daily treatment was 1.2 (95 percent confidence interval, 1.0 to 1.6). Figure 1 shows the estimated survival distribution according to treatment group.

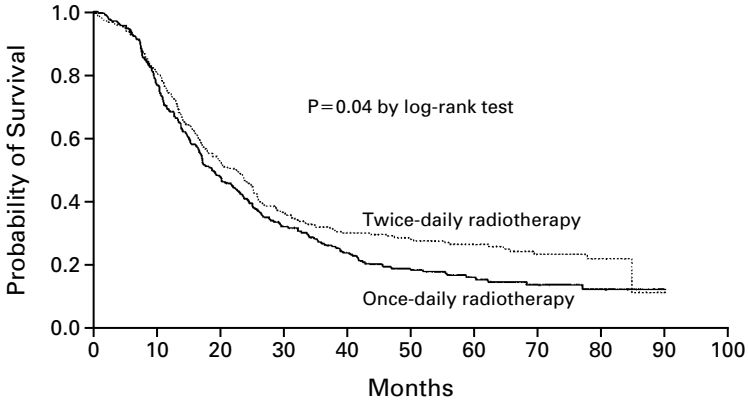
The rate of failure-free survival at two years was 24 percent for patients receiving once-daily therapy and 29 percent for those receiving twice-daily therapy ($P=0.10$). According to a proportional-hazards regression model, male sex ($P=0.01$) and a performance status of 2 ($P=0.005$) were associated with shorter failure-free survival.

Pattern of Treatment Failure

Twice-daily thoracic radiotherapy reduced the rate of local failure: the rate was 52 percent in the group receiving once-daily therapy and 36 percent in the group receiving twice-daily therapy ($P=0.06$). The rates of simultaneous local and distant failure were significantly different between the groups: both local and distant failure occurred in 23 percent of the patients receiving once-daily therapy and 6 percent of those receiving twice-daily therapy ($P=0.01$).

DISCUSSION

In this trial of chemoradiotherapy for small-cell lung cancer, we gave four cycles of cisplatin–etoposide chemotherapy concurrently with 45 Gy of thoracic radiation administered twice daily or once daily. The survival rate among the 417 patients exceeded that in any previously reported large, randomized trial of chemotherapy and radiotherapy for this disease.[19-24] After five years of follow-up, only 335 deaths have been reported, even though 353 deaths were anticipated at two years. Survival was significantly better in the group receiving twice-daily radiotherapy than in the group receiving once-daily radiotherapy ($P=0.04$). The magnitude of the difference between the groups at two years was quite small and clinically insignificant, but with further follow-up to five years, the difference between the treatments favored the twice-daily treatment group by 10 percent (standard error, 4 percent).



Treatment Group	0–20 Mo	20–40 Mo	40–60 Mo	60–80 Mo	80–100 Mo
	no. of deaths/no. at risk				
Once daily	108/206	48/96	15/47	4/21	0/5
Twice daily	100/211	47/109	7/62	5/42	1/14

Figure 1. Kaplan–Meier Estimates of Overall Survival for All 417 Patients Assigned to Treatment Groups.

Many assert that adding thoracic radiotherapy to chemotherapy increases toxicity without improving survival. A meta-analysis of chemotherapy alone as compared with chemotherapy and radiotherapy found that the addition of radiotherapy improved the survival rate at three years only slightly.[2] The trials included in the meta-analysis all used cyclophosphamide-based or doxorubicin-based regimens; in none did initial treatment include cisplatin and etoposide.

Although it was introduced in the late 1970s,[25,26] the combination of cisplatin and etoposide emerged as primary therapy only in the early 1980s.[4,9] A clear advantage of cisplatin plus etoposide is that the combination can be given concurrently with relatively full doses of thoracic radiotherapy, with less morbidity than occurs with doxorubicin-based[27,28] or cyclophosphamide-based[29] regimens. The meta-analysis[2] identified no differences regarding the timing of thoracic radiotherapy and chemotherapy.

The best method of integrating chemotherapy and thoracic radiotherapy remains unknown. Because small-cell lung cancer responds well to thoracic radiotherapy, only moderate doses of radiation (40 to 50 Gy) have been used in most trials. Choi et al.[30] reported that esophagitis limited treatment when the total dose from twice-daily treatment exceeded 45 Gy, and that a total dose of 70 Gy could be tolerated with once-daily treatments. Papac and colleagues[31] reported a rate of local failure of only 3 percent with 60 Gy fractionated once daily, but with only a small gain in median survival. Without radiotherapy, local failure occurs in 90 percent of patients.[24] Our study verifies that local failure remains an important problem, but we found that improved local therapy contributes to both local control and survival.

The timing of concurrent radiotherapy and chemotherapy may be an important therapeutic variable. We initiated therapy at the same time as the first cycle of cisplatin plus etoposide. Others have begun radiotherapy at the time of later cycles of chemotherapy. Murray et al.[23] reported that cisplatin–etoposide therapy in combination with radiotherapy beginning with cycle 2 was superior to concurrent radiotherapy beginning with cycle 6. Recently, Takada and colleagues[32] verified that beginning radiotherapy concurrently with etoposide was superior to beginning radiotherapy after the completion of four cycles of chemotherapy. The Cancer and Leukemia Group B trial compared radiotherapy starting with cycle 1 of chemotherapy and radiotherapy starting with cycle 4.[24] This 1987 trial used cyclophosphamide-based chemotherapy. It found the best survival when the radiotherapy began with cycle 4. Others, particularly in Europe,[21,22] found that sequential strategies were superior to concurrent treatment, which was associated with excess toxicity. Cyclophosphamide-based or doxorubicin-based chemotherapy continues to be used in these studies, which may explain the inability to integrate concurrent thoracic radiotherapy successfully. The two-year survival in these trials is about half the rate in our study.

The number of deaths we initially projected to occur in two years has not occurred after a minimal follow-up of five years. Esophagitis after twice-daily radiotherapy did not lead to stricture, and all the affected patients recovered their ability to swallow. Only 1 death was attributable to hematologic toxicity, and there were only 11 treatment-related deaths. Although there was an imbalance in age between the groups, age did not influence survival significantly when isolated as a variable (data not shown).

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