ORIGINAL ARTICLE

# Local Control and Toxicity of Adaptive Radiotherapy Using Weekly CT Imaging: Results from the LARTIA Trial in Stage III NSCLC

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**ABSTRACT**

**Introduction:** Anatomical change of tumor during radiotherapy contributes to target missing. However, in the case of tumor shrinkage, adaptation of volume could result in an increased incidence of recurrence in the area of target reduction. This study aims to investigate the incidence of failure of the adaptive approach and, in particular, the risk for local recurrence in the area excluded after replanning.

**Methods:** In this prospective study, patients with locally advanced NSCLC treated with concomitant chemoradiation underwent weekly chest computed tomography simulation during treatment. In the case of tumor shrinkage, a new tumor volume was delineated and a new treatment plan outlined (replanning). Toxicity was evaluated with the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer scale. Patterns of failures were classified as *in field* (dimensional and/or metabolic progression within the replanning planning target volume [PTV]), *marginal* (recurrence in initial the PTV excluded from the replanning PTV), and *out of field* (recurrence outside the initial PTV).

**Results:** Replanning was outlined in 50 patients selected from a total of 217 patients subjected to weekly simulation computed tomography in our center from 2012 to 2014. With a median follow-up of 20.5 months, acute grade 3 or higher pulmonary and esophageal toxicity were reported in 2% and 4% of cases and late toxicity in 4% and 2%, respectively. Marginal relapse was recorded in 6% of patients, and 20% and 4% of patients experienced in-field and out-of-field local failure, respectively.

**Conclusions:** The reduced toxicity and the documented low rate of marginal failures make the adaptive approach a modern option for future randomized studies. The best scenario to confirm its application is probably in neo-adjuvant chemoradiation trials.



*Keywords:* Adaptive radiotherapy; Locally advanced; NSCLC; Chemoradiation; Intrathoracic changes

## Introduction

Concurrent chemoradiation is the standard of care for patients affected by locally advanced (LA) NSCLC. Its superiority over radiotherapy alone or sequential chemoradiation has been proved in multiple phase III randomized trials.[1–5] In a meta-analysis of six randomized studies, concurrent chemoradiotherapy decreased locoregional progression by 6.1% at 5 years when compared with sequential chemoradiation.[6] This resulted in an improvement in overall survival of 4.5% at 5

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years that was possibly directly related to locoregional control. Many patients however succumb to locoregional failure or distant metastases.[7]

Radiation Therapy Oncology Group (RTOG) 0617 reported the highest survival in phase III trial with concomitant chemoradiation in a radical setting with application of a standard dose of radiation.[8] However, the subsequent vast literature debate highlighted problems linked to the trial,[9,10] which failed to demonstrate the superiority of the dose escalation strategy over standard doses and for which even in the winning arm, some data, such as nonhematologic toxicity grade 3 (G3) or higher in 58% of patients, are not negligible.

Thanks to modern radiotherapy techniques, some strategies manage the geometrical uncertainties of imaging, treatment planning, and treatment delivery and thereby improve target coverage with a much steeper dose gradient and less irradiated normal tissue.[11–13]

Some approaches apply altered fractionation to deliver a higher biologically effective dose without prolonged overall treatment time,[14,15] whereas others consider the possibility of delivering a higher dose to the biological target volume[16,17] concurrently or sequentially to the irradiation of the entire gross tumor volume (GTV).

The introduction of image-guided radiotherapy reveals the occurrence of target changes during treatment, and although the percentage of patients who experienced regression is not high (range 25%–40%), the degree of regression is in the range of 29% to 40%, corresponding to a rate of tumor shrinkage per fraction of 0.79% to 1.65%.[18–24] Anatomical changes during radiotherapy might introduce discrepancies between the planned and delivered dose. As demonstrated, replanning in the case of a GTV decrease of 30% or more is linked with lower normal tissue constraints.[25] Although adapting dose distribution to the new target can lead to improved results, the safety of applying routine replanning in patients with tumor shrinkage has not been confirmed. Concern has been raised about the idea that some microscopic tumor cells can survive around the reduced target and lead to increased local failure in areas underdosed by replanning[26] and about the fact that this method is time-consuming. Currently, the literature reports only dosimetric experiences and lacks clinical data on outcome when patients are treated with the adaptive approach.

This study aims to investigate the failure pattern in patients with LA NSCLC treated with concurrent chemoradiotherapy with an adaptive approach, in particular, to evaluate the risk for local recurrence in the area excluded during replanning.

## Methods and Materials

### *Patient Selection*

In this prospective study patients with LA NSCLC treated with concurrent chemoradiation at our institution from 2012 to 2014 were enrolled. The inclusion criteria were radical treatment; histologically or cytologically proven NSCLC; inoperable stage IIIA/IIIB disease and intrathoracic relapse after surgery; positron emission tomography (PET)/computed tomography (CT) and/or total-body CT with contrast excluding metastatic disease (including brain); no previous radiotherapy treatment; Eastern Cooperative Oncology Group performance status of 0 to 1; clinically measurable/evaluable disease; minimum life expectancy of 12 weeks; adequate respiratory, renal, hepatic and bone marrow function; and noncontraindicative cardiovascular disease. The exclusion criteria were concurrent systemic disorders incompatible with chemotherapy or radiotherapy. The protocol was approved by the department board and ethical committee of Campus Bio-Medico University, with patients' written informed consent.

### *Treatment: Radiotherapy Preparation and Chemotherapy Regimen*

Patients were immobilized with customized devices. Either four-dimensional CT or slow CT images using a multislice CT scanner were acquired to evaluate internal target motion. Initially, GTV was determined in the maximum intensity projection on the initial size of the tumor and involved lymph nodal sites defined as PET-positive nodes and/or a node diameter greater than 1 cm, clinical target volume (CTV) was defined as equal to the GTV plus node-positive stations and hilar stations, and planning target volume (PTV) was created equal to the CTV plus a 0.5-cm safety margin.

Treatment was performed with a linear accelerator (Varian Medical System) in a photon regimen, with a 6- to 15-MV nominal energy and three-dimensional (3D) conformal technique according to location with multiple planar and nonplanar beams.[27] The total prescribed dose was delivered with conventional fractions (5 d/wk) in a daily dose of 180 cGy and was specified at a representative point in the PTV, with 95% of the PTV to be covered by 95% to 105% isodoses. The planning constraints for organs at risk were as follows: lung parenchyma $V_{20}$ less than 30%, $V_{30}$ less than 15%, mean lung dose less than 20 Gy, and $V_{20}$ ipsilateral less than 52%[28]; spinal cord maximum dose 40 Gy; esophagus $V_{45}$ less than 40% and mean dose less than 34 Gy; total heart dose 40 Gy or less, with two-thirds of the heart receiving 50 Gy or less and one-third receiving 66 or less. Concurrent chemotherapy regimens were platinum-based

doublets (cisplatin-gemcitabine/carbotaxol) or monotherapy (gemcitabine or pemetrexed).

During treatment all patients underwent weekly chest CT simulations without intravenous contrast to assess acute toxicity and tumor shrinkage, and they were all visualized by two radiation oncologists independently. A mean of five CT simulations in addition to the initial simulation CT were performed for each of the 217 patients, for a total of 1100 examinations. For all CT simulations, each physician was able to judge whether reduction was (1) present and clinically significant (which could also have meant that the reduction did not occur over a predetermined percentage but the area where it occurred could reduce the dose to the lung parenchyma), (2) present and clinically nonsignificant, or (3) absent. In the case of physician agreement for the first category, a contrast-enhanced CT was performed to better visualize node reduction, a new target volume was delineated (Fig. 1), and a new treatment plan (replanning study) was performed. Patients were treated without any time break.

## Side Effects

Tolerability evaluation was performed weekly during treatment with a clinical visit, blood samples, and CT simulation imaging used to report early lung parenchyma damage in asymptomatic patients; thereafter, CT imaging with contrast was performed 45 days after the end of treatment, every 3 months during the first year, every 4 to 6 months for 2 years, and subsequently according to the standard follow-up protocol. Acute toxicity was evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0. Late events were registered according to the RTOG/European Organization for Research and Treatment of Cancer late radiation morbidity scoring schema.

**Hematologic Toxicity.** Chemotherapy administration was postponed if the white blood cell count was less than $2.5 \times 109$/L and/or the platelet count was $90 \times 109$/L or lower and/or the hemoglobin level was less than 10 g/dL. In the case of G3 toxicity, radiochemotherapy treatment was interrupted, and when the suspension lasted more than 7 days, the treatment was stopped.

**Nonhematologic Toxicity.** Grade 2 (G2) or higher pulmonary damage was managed with treatment interruption; treatment was either restarted once symptoms had disappeared or stopped. If symptomatic (e.g., cough, dyspnea) or radiographic (pneumonia) pulmonary toxicity arose, corticosteroids, antibiotics, and bronchodilator aerosol therapy were administered. The need for oxygen therapy was also evaluated. In the event of onset of esophagitis, to prevent worsening symptoms, some suggestions about diet were given to the patients. For grade 1 esophageal toxicity, sucralfate solution was orally administered; for G2 and higher esophageal toxicity, anti-inflammatory and opioid drugs were administered; and for G3 esophagitis, treatment was stopped until resolution.

## Patterns of Failure and Outcome

Recurrences were identified visually and independently by three radiation oncologists with the same method reported in a previous publication.[29] The modality for definition of failures was readjusted with these definitions: *in-field* failure when a dimensional and/or metabolic progression was reported within the replanning PTV; *marginal* failure in cases of recurrence in the initial PTV but not in the replanning PTV, and *out-of-field* failure if the recurrence occurred outside the initial PTV. Local recurrences were defined according to a dimensional and metabolic increase at chest CT with intravenous contrast and fludeoxyglucose F 18 (FDG) PET/CT. Response evaluation was defined according to the Response Evaluation Criteria in Solid Tumors criteria for complete and partial response, progression, and stable disease. Distant failure, overall survival, and progression-free survival were also reported.

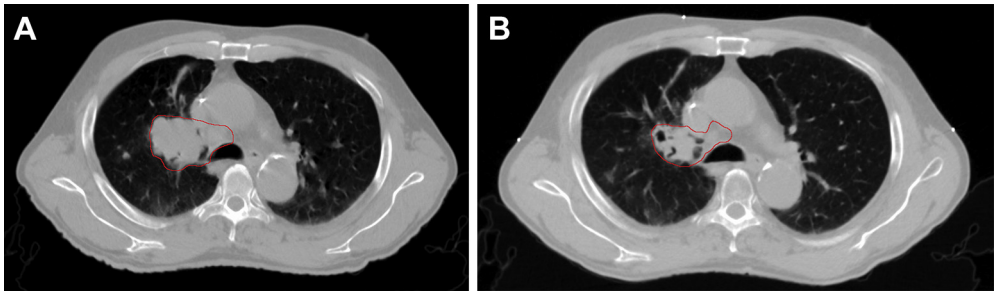


**Figure 1.** (*A*) Tumor volume delineation at first computed tomography simulation. (*B*) Reduced target volume at replanning computed tomography scan.

### Statistical Analysis

The study was planned to obtain a 66% reduction in late G3 or higher toxicity in comparison with RTOG 9410.[5] In that trial G3 or higher late pulmonary toxicity was reported in 13% and 17% of patients treated with concurrent chemoradiation with standard and hyperfractionation, respectively. With $\alpha$ equal to 0.05 and power equal to 80%, the sample size was calculated in 49 patients.

The time-to-event curve was calculated by the Kaplan-Meier method for time to local failure, progression-free survival, and overall survival. The differences between chemotherapy groups were compared by Fisher's exact test (two tail) or Student's $t$ test when appropriate. $p$ Values of 0.05 or lower were considered statistically significant.

## Results

Replanning was outlined in 50 patients selected from a total of 217 patients subjected to weekly simulation CT in our center from 2012 to 2014. Patient characteristics are shown in Table 1. The mean age was 69.6 years (range 38–92), the squamous histologic subtype was reported in 56% of patients, and stage IIIA disease was reported in 58% of cases. The median total dose delivered was 66 Gy (range 45–75 Gy), with standard fractionation and concurrent chemotherapy administrated in all patients. The mean OTT for the whole group was 54 days even if this result was conditioned by the treatment purpose (neoadjuvant versus radical).

**Table 1.** Patient Characteristics

| | Patients n (%) |
|---|---|
| Total | N = 50 (100%) |
| Age, y | |
| Mean + SD | 69.6 + 10.4 |
| Range | 38-92 |
| Sex | |
| Male | 39 (78%) |
| Female | 11 (22%) |
| Histologic subtype | |
| Squamous | 28 (56%) |
| Adenocarcinoma | 16 (32%) |
| NOS | 3 (6%) |
| No histologic subtype available | 3 (6%) |
| Clinical stage | |
| IIIA | 29 (58%) |
| IIIB | 21 (42%) |
| Induction chemotherapy | |
| Yes | 23 (46%) |
| No | 27 (54%) |
| Concurrent chemotherapy | |
| Platinum-based doublet | 19 (38%) |
| Gemcitabine alone | 24 (48%) |
| Pemetrexed alone | 7 (14%) |

NOS, not otherwise specified.

With a mean follow-up of 25.8 months, G2 acute pulmonary and esophageal toxicity were reported in 20% and 26% of patients, respectively. G3 or higher toxicity was reported in 2% and 4% of cases, respectively. G3 or higher late pulmonary and esophageal toxicity was reported in 4% and 2% of patients, respectively.

The primary end point of the study was reduction of G3 or higher pulmonary toxicity in comparison with 13% to 17% reported in RTOG 9410. In the present study the rates of acute and late G3 or higher pulmonary toxicity were 2 and 4% respectively, thus the study matches its primary end-point.

A mean initial and replanning CTV of 154.9 $cm^3$ (SD = 117 $cm^3$) and 90.7 $cm^3$ (SD = 71.7 $cm^3$) was reported, with an average CTV shrinkage of 42% (range 15%–67%) between the simulation CT and replanning CT (Table 2). The median dose for target replanning was 45 Gy (range 19.8–59.4 Gy). The mean CTV reduction in patients treated with or without full-dose cisplatin favored the first group (97.7 versus 55.8 $cm^3$ [$p = 0.02$]). No differences in tumor reduction were found between patients treated with or without induction chemotherapy before concomitant chemoradiation (66.4 $cm^3$ versus 61.6 $cm^3$, corresponding to 40.8% versus 44% [$p = 0.76$]).

Reevaluation imaging was not performed on two patients (79 and 84 years old) on account of progressive deterioration of clinical conditions. A total of 48 patients were eligible to be evaluated for response, and at first follow-up two complete responses (4.1%), 33 partial responses (68.8%), and 13 cases of stable disease (27.1%) were recorded.

Seven local, 14 distant, and eight simultaneous local and distant failures occurred, with a total of 30% of patients experiencing local failure. Local failures were in-field, marginal, and out-of-field in 20%, 6%, and 4% of cases, respectively. Figure 2 shows the three marginal failures. The recurrence contours are overlapped with the replanning CT simulation. The distribution of the dose equal to 95% of the prescribed dose in the initial planning, replanning, and plan sum for one of the three patients experiencing the marginal failure is illustrated in Figure 3. In two of these three patients, distant metastasis was documented concurrently with the diagnosis of marginal recurrence. The planning data of patients with marginal relapse are reported in Table 2. The volume of the failure receiving 95% of the prescribed dose ranged from 30.1% to 65.3% and the range of the total dose covering 100% of the failure volume was 42.5 to 49.1 Gy. The initial mean CTV was higher in

**Table 2.** Marginal Failures: Patient Characteristics and Planning Data

| Patient | Sex | Age | Stage | ΔCTV, % | Total RT dose, Gy | $FV_{95\%}$, % | $FD_{100\%}$, Gy |
|---|---|---|---|---|---|---|---|
| 1 | M | 67 | IIIA | 33.9 | 59.4 | 50 | 47.3 |
| 2 | M | 72 | IIIB | 46.6 | 70.2 | 30.1 | 42.5 |
| 3 | M | 62 | IIIB | 35.6 | 70.2 | 65.2 | 49.1 |

CTV, clinical target volume; RT, radiotherapy; $FV_{95\%}$, volume of the failure receiving the 95% of the prescribed dose; $FD_{100\%}$, total dose covering the 100% of the failure volume.

patients with local relapse than in those who did not experience local relapse (167.9 $cm^3$ and 146.4 $cm^3$), even if the difference was not statistically significant. Moreover, none of the other variables included in the univariate analysis (age, sex, total dose, concurrent chemotherapy regimen, and induction chemotherapy) affected the local recurrence rate.

The median time to local failure, progression-free survival, and overall survival (Fig. 4) were 8.5, 8.3, and 30.5 months, respectively. The median onsets of marginal, in-field, and out-of-field recurrences were 12, 9.2, and 7.1 months, respectively.

## Discussion

Tumor regression during chemoradiation appears approximately in one out of three cases[18,24,30] when a morphologic criterion is adopted, whereas this rate is up to 70% if the metabolic tumor volume on PET is considered.[31] Several reports have investigated this and others types of changes,[18–25] but to the best of our knowledge, our study is the first to report the clinical outcome of the adaptive approach in the case of morphologic reduction in tumor volume. A low rate of pulmonary toxicity (2% and 4% of acute and late ≥G3 lung damage) and a nonincreased rate of local failure (30%) have been documented in this trial. These encouraging results confirm the adaptive approach as a promising strategy to improve outcome in combined treatment for LA disease.

Several strategies to improve outcome in radical chemoradiation have been proposed. Standard fractionated dose escalation seems outdated by RTOG 0617, but the overall survival time of 28.7 months in the standard arm is one of the highest ever reported in a multicenter phase III trial.[8] However, the rates of G3 or higher nonhematologic toxicity were 58% and 62% in the standard and high-dose arms, respectively, and G3 or higher pneumonitis was reported in 8% of patients treated with the 3D technique. In the same article, a statistically significant reduction to 3.5% was reported in case of application of the intensity-modulated radiation therapy technique.[32] As is known, intensity-modulated radiation therapy has been associated a higher value of $V_5$ than 3D conformal radiotherapy (55% versus 62% [$p < 0.001$]), and whether low-dose bath predicts radiation pneumonitis is still controversial today.[33,34] Adaptive radiation therapy overcomes this problem by leading to a reduction in all dosimetric constraints; in fact, it has been reported that with plan adaptation, the mean lung dose is reduced by 5% to 7.9%.[35] In the present clinical report, G3 or higher lung toxicity with use of 3D conformal radiotherapy is lower than in RTOG 0617 (2% versus 8%), attesting to the ability of this strategy to ensure a good therapeutic index even in comparison with the modern radiotherapy techniques. Our results are even more significant if we look at the lung toxicity rate of the RTOG 9410 concurrent arms (≥G3 toxicity rates of 13% and 17% in the standard and hyperfractionated arms, respectively).[5]

In addition to the low incidence of toxicity, we observed that relapses are not increased in comparison with the literature data. The local failure rate of 30% is

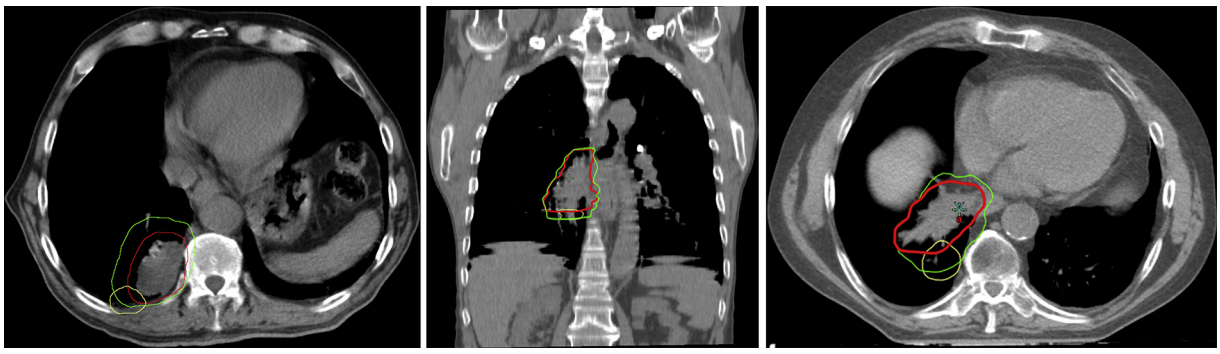

**Figure 2.** Marginal failures imaging: initial planning target volume (*green*), replanning planning target volume (*red*), and recurrence contour (*yellow*).

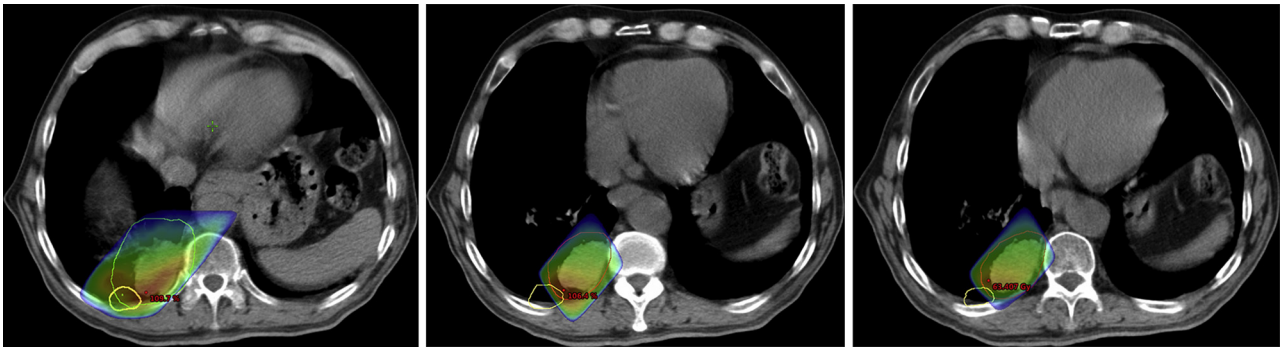

**Figure 3.** Dose distribution of 95% of the prescribed dose in the initial planning, replanning, and plan sum for one of the three patients experiencing the marginal failure (*yellow*).

highly comparable to that reported by others: RTOG 9410 reported local failure rates of 33% and 25% in the standard and hyperfractionated arms, respectively[5]; in the standard and higher-dose arms of RTOG 0617, the respective rates were 31% and 38%[8]; and in the PROCLAIM trial, the percentage reached 40%.[36] The most common pattern of failure in our adaptive strategy was in-field recurrence, and the low rate of marginal failure found in our series (6%) could be interpreted as clinical confirmation of a previous retrospective planning study.[37] These authors simulated influence of an adaptive approach on dose distribution in areas of microscopic disease (MD) and calculated the tumor control probability in two different scenarios: shrinkage of the MD synchronously with the GTV and stationary MD disease within the lung despite tumor shrinkage. The authors of the previous retrospective planning study concluded by affirming that "adaptation of radiotherapy to the shrinking GTV (in both scenarios) did not compromise dose coverage of volumes of suspect microscopic disease and has the potential to increase tumor control probability by >40% compared with radiotherapy planning without adaptive therapy."[37] In the present study, the mean tumour shrinkage was 42%. In others studies examining 3D or volumetric modulated arc therapy experiences were reported, with tumor

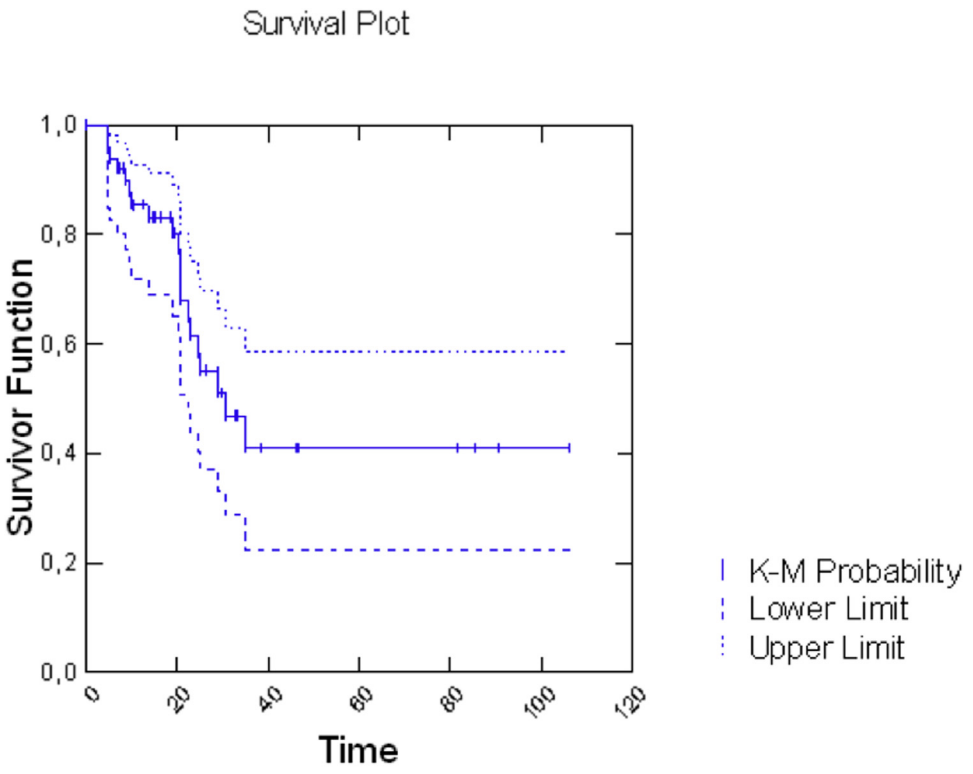


**Figure 4.** Overall survival curve (in months) with upper and lower limits. K-M, Kaplan-Meier.

reduction ranging from 29% to 40%,[19–21,24–25,38] which corresponds to a tumor shrinkage rate of 0.79% to 1.65% per fraction.

In our series the median dose for target replanning was 45 Gy (25 fractions of 1.8 Gy/d). The best momentum to obtain the maximum gain has been estimated at 15 to 20 for fractions of 2 Gy/d,[39,40] even if there are some data showing a progressive GTV reduction increasing total dose (24.7% at 30 Gy and 44.3% at 50 Gy).[20] Tumor volume reduction was improved by the chemotherapy regimen administered during radiotherapy, with the higher rate of shrinkage reached with a cisplatin-based doublet. Moreover, sequential treatment needs higher doses to obtain the same volume reduction in comparison with concurrent chemoradiation.[39,41] This could be due to previous tumor shrinkage during chemotherapy and/or accelerated tumor repopulation[42] triggered by upfront chemotherapy followed by radiotherapy only.

The interest in the clinical outcome of the adaptive strategy is also documented by the rapid accrual of an RTOG study (RTOG 1106/ACRIN 6697), a randomized phase II trial of individualized adaptive radiotherapy (ART) using during-treatment FDG-PET/CT and modern technology in LA NSCLC in which the primary objective is to determine whether tumor dose can be escalated to improve the local recurrence progression-free survival rate at 2 years when an individualized adaptive radiation treatment plan is applied by the use of a FDG-PET/CT scan acquired at 40 to 46 Gy. During the wait for these results, our prospective and clinical data add knowledge to the field.

In the present study some limitations can be highlighted. First of all, the omission of breathing motion in our calculations is a limit, but as reported in other trials,[39] anatomical changes have usually resulted in larger dosimetric changes than both respiratory motion and baseline shifts.[43] Rigid fusion to calculate cumulative doses to organs at risk and target volume was used, although deformable registration could produce better dosimetric calculations. It could be speculated that only 50 of 217 patients could benefit from the adaptive strategy during treatment. A quantitative cutoff point for replanning was not applied, and the decision for redelineation and replanning was made on the basis of two radiation oncologists agreeing in considering the reduction of the tumor volume clinically significant. Taking into account that a mean of five CT simulations were performed for each of the 217 patients, the delineation of 1100 examinations was considered too time-consuming. Even though it was not the primary end point of the present trial, GTV delineation of all weekly CTs in all patients could provide more objective data and could be investigated in the future. An outcome comparison with patients for whom replanning was not performed is certainly an interesting topic; however, after an in-depth discussion between authors, the choice was to invest efforts to plan a phase III trial (actually in preparation) randomizing between ART and no ART in shrinking patients' tumors rather than in collecting retrospective data.

Finally, our method facilitated the attainment of careful delineation of malignant lymph nodes thanks to simulation- and contrast-enhanced CT scans, even though this would not be feasible in the case of a cone beam CT–based adaptive strategy.[39]

Even if more complex radiation planning and quality assurance are unquestioned in an adaptive strategy, the possibility of reducing toxicity rather than "whole tumor" radiotherapy treatment, as well as the documented low rate of marginal failures, makes this approach a modern option for future randomized studies. In conclusion, the clinical experience with replanning is positive, has resulted in reduced toxicity, and has not led to excessive local recurrences in selected patients.

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