Three-times Daily Radiotherapy after Chemotherapy in Stage III Non-small Cell Lung Cancer. Single-institution Prospective Study

GIANPIERO CATALANO[1], TOMMASO DE PAS[2], LORENZO SPAGGIARI[3,5], SARA GANDINI[4], BARBARA ALICJA JERECZEK-FOSSA[1,5], FILIPPO DE BRAUD[2], FRANCESCO LEO[3], GIULIA VERONESI[3] and ROBERTO ORECCHIA[1,5]

Divisions of [1]Radiotherapy, [2]Medical Oncology – New Drugs Development Unit, [3]Thoracic Surgery, [4]Epidemiology and Biostatistics, European Institute of Oncology, Milan; [5]University of Milan, Italy

Abstract. *Aim: A prospective study for stage IIIA-B non-small cell lung cancer (NSCLC), with three-times daily (3td) radiotherapy (RT), after induction chemotherapy (iCT), with or without surgery. Patients and Methods: Induction cisplatin and gemcitabine chemotherapy was delivered. Surgery and postoperative (post-op) radiotherapy were planned for responsive stage IIIA patients; definitive irradiation was performed in unresectable IIIA and IIIB patients. Doses of 54.4 and 64.6 Gy were delivered for the post-op and definitive treatments, respectively. Results: Out of 52 patients (pts), 37 received 3tdRT as definitive (18 pts) or post-op treatment (19 pts). Overall, the failures were similar between post-op and definitive 3tdRT (78.9% vs. 77.8%). In the post-op treatment, metastases and local failures were 52.6% and 10.5%, respectively and in the definitive radiotherapy, the incidence was similar (local 33.3% vs. systemic 44.4%). The five-year overall survival (OS) was 25% for the post-op and 21% for the definitive patients (p=0.87). Conclusion: Three-times daily postoperative radiotherapy did not improve the outcome in NSCLC, but for unresectable patients, this approach may have a role in selected cases.*

For locally advanced non-small cell lung cancer (NSCLC), the high rate of metastasis requires chemotherapy (CT) integration with local treatments, especially in cases of mediastinal involvement, an accepted unfavourable prognostic factor (1), where evidence supports induction chemotherapy (iCT) before surgery (2-5). Since resection may sometimes be debatable or not indicated (large N2 or N3 class), and since some patients (pts) may be unfit for surgery for medical reasons, radiotherapy (RT) is often an alternative treatment (6). To date, unconventional RT schedules have been tested with encouraging results to increase local control (7-9). As far as integrated treatments are concerned, concomitant chemoradiation has been shown to be an effective strategy (10-12); nevertheless, it has resulted in higher toxicity (13-16). Thus, sequential treatment has often been performed (17-20).

The long-term results of a prospective study investigating three-times daily RT (3tdRT) after iCT in NSCLC with histologically confirmed mediastinal involvement are reported.

Correspondence to: Dr. Gianpiero Catalano, European Institute of Oncology, via Ripamonti 435, 20141 Milano, Italy. Tel: +39 0257489037, Fax: +39 0294379227, e-mail: gianpiero.catalano@ieo.it

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Patients and Methods

The treatment and patient characteristics have been previously described (21). Three cycles of cisplatin and gemcitabine, repeated every 3 weeks, were scheduled in mediastinoscopy-based stage IIIA(N2)-IIIB NSCLC pts, unless disease progression (PD) or severe toxicity occurred. The response was evaluated after two cycles (22). The resectable IIIA pts, without PD, underwent surgery and postoperative (post-op) 3tdRT; the IIIB and unresectable IIIA pts, underwent definitive 3tdRT. Metastatic pts were excluded from the study. The 3tdRT doses were 54.4 Gy and 64.6 Gy for post-op and definitive pts, respectively; the doses were delivered in three-daily fractions of 1.2 Gy, 1 Gy and 1.2 Gy, with a minimal inter-fraction interval of 5 hours, five days a week, according to the Linear Quadratic Model (23). The "Concomitant Boost" technique was used as follows. A "large" volume was irradiated *via* opposed anterior-posterior fields, in the first and third daily fraction, up to 38.4 Gy. This volume consisted of the pre-iCT gross disease and elective bilateral mediastinal irradiation, with a 1-2 cm safety margin; for upper lobe tumors, the ipsilateral supraclavicular nodes were treated. In the second daily fraction, a "boost" volume, limited to the gross tumor volume (plus a 1.5 cm margin), was treated with "off-cord" fields, up to an additional 16 Gy. In the definitive group, after 54.4 Gy treatment was continued on "boost" volume only,

three times a day, up to 64.6 Gy. The schedule followed the International Committee of Radiation Units Report 50 recommendations (24).

Follow-up started four weeks after treatment and continued every four months unless an unexpected clinical event occurred. RT acute and late toxicities were scored according to Radiation Therapy Oncology Group (RTOG) / European Organization for Research and Treatment of Cancer (EORTC) System. The hospital Ethical Committee approved the study and all the pts gave informed consent.

The primary study objective was to determine if an intensive locoregional approach, with 3tdRT, combined with standard treatment, should be investigated in a Phase II study. The primary end-point was local progression; secondary end-points were PD (local or distant) and overall survival (OS). The study was designed to detect local PD, as the sole pattern of failure, of 20% compared with a maximal, clinically unacceptable local progression of 45%, adopting the 3tdRT after iCT in NSCLC. A sample size of 37 pts would achieve 90% power to detect a difference of 25% using a two-sided binomial test. The target significance level was 0.05. Statistics and frequency tables data are given whenever appropriate. Survival-time was computed from the first iCT cycle to the date of event occurrence; in event-free individuals, the observation-time was recorded at the last follow-up. The OS curves were obtained with the Kaplan-Meier method. The log-rank test was used to compare survival between groups. Differences with a p-value ≤ 0.05 were considered statistically significant. Statistical analyses were performed with the SAS package, version 8.2 (SAS Institute, Cary, NC, USA).

Results

From February 1998 to October 2000, 52 pts (39 IIIA, 13 IIIB) were enrolled (Table I, Figure 1). Radical surgery was performed in 25 pts (19 lobectomies, 5 pneumonectomies and 1 segmentectomy). In 5 pts, surgical complications occurred (1 adult respiratory distress syndrome, 4 heart failure), all recovered. 3tdRT was performed in 19 of the radically resected IIIA, 1 not radically resected IIIA, 5 non-resected IIIA and 12 IIIB pts. Thus, 37 pts underwent 3tdRT (18 definitive, 19 post-op). 3tdRT was not performed in 15 pts, due to progressive disease (10 pts), protocol violation (4 pts) and surgical morbidity (ARDS) in one patient. All but one pt reached the planned dose (one post-op patient stopped at 51 Gy). Acute 3tdRT toxicity was mainly esophagitis, grade 2 (RTOG) in 25 pts (67.6%) and grade 3 in 4 pts (10.8%) (21). All but seven pts died, two pts were lost to follow-up after 8 and 28 months, respectively.

The failure patterns were evaluated for all 52 pts and in the 3tdRT subgroup (37 pts). In the whole group, 42 PD occurred (14 local, 25 systemic, 2 local + systemic, 1 unknown), seven pts were free of disease at last follow-up (Table II). In the 37 irradiated pts, 29 PD occurred (8 local, 18 systemic, 2 both, 1 unknown). The failure patterns were also stratified between post-op and definitive 3tdRT with no difference between groups (78.9% *vs.* 77.8%, respectively). In the post-op 3tdRT pts local failure occurred in 4 out of 19 irradiated pts (21%), with higher incidence of distant metastases (Table II). In the definitive 3tdRT group, the rate of local and systemic PD were 33.3% and 44.4%, respectively. Brain failures were equal in the two groups: 3/12 in the post-op (25% of distant relapses) and 2/8 in the definitive 3tdRT (25% of distant PD).

The median OS and 2-year and 5-year OS rates were 15 months, 40% and 19%, respectively (Table III). For stage IIIA and IIIB, 2-year and 5-year OS were 44% and 19% and 26% and 17%, respectively (Figure 2), without any statistical difference (p=0.78 at 5 years). No differences were demonstrated for surgery, response to iCT, pathological N2 stations or clinical stage (Table III, Figure 2).

In the 3tdRT pts, the 2-year and 5-year OS was 55% and 25% for the post-op pts *vs.* 42% and 21% for the definitive pts, respectively (Table III, Figure 3).

Table I. *Patient and disease characteristics.*

Characteristic	Number of patients	Percentage
Age (years)		
Median	58 (range 40-75)	
Gender		
Male	40	77%
Female	12	23%
KPS†		
Median	90 (range 70-100)	
Histology		
Squamous cell	26	50%
Adenocarcinoma	19	36%
Other NSCLC	4	8%
NSCLC not specified	3	6%
Clinical TNM		
T_{1-2} N_2	29	
T_3 N_2	10	
T_4 N_2	3	
T_{1-2} N_3	6	
T_3 N_3	4	
Pathological TNM*		
yT_1 N_0	2	
yT_{1-2} N_1	2	
yT_{3-4} N_1	2	
yT_{0-2} N_2	16	
yT_3 N_2	2	
yT_2 N_3	1	
Resected total lymph nodes*		
Median	20 (range 5-40)	
Resected mediastinal lymph nodes*		
Median	12 (range 2-25)	
Involved N2 stations*		
Median	2 (range 0-4)	
Involved N2 lymph nodes*		
Median	3 (range 0-14)	

†KPS, Karnofski performance status; *referred only to completely resected stage IIIA patients (25).

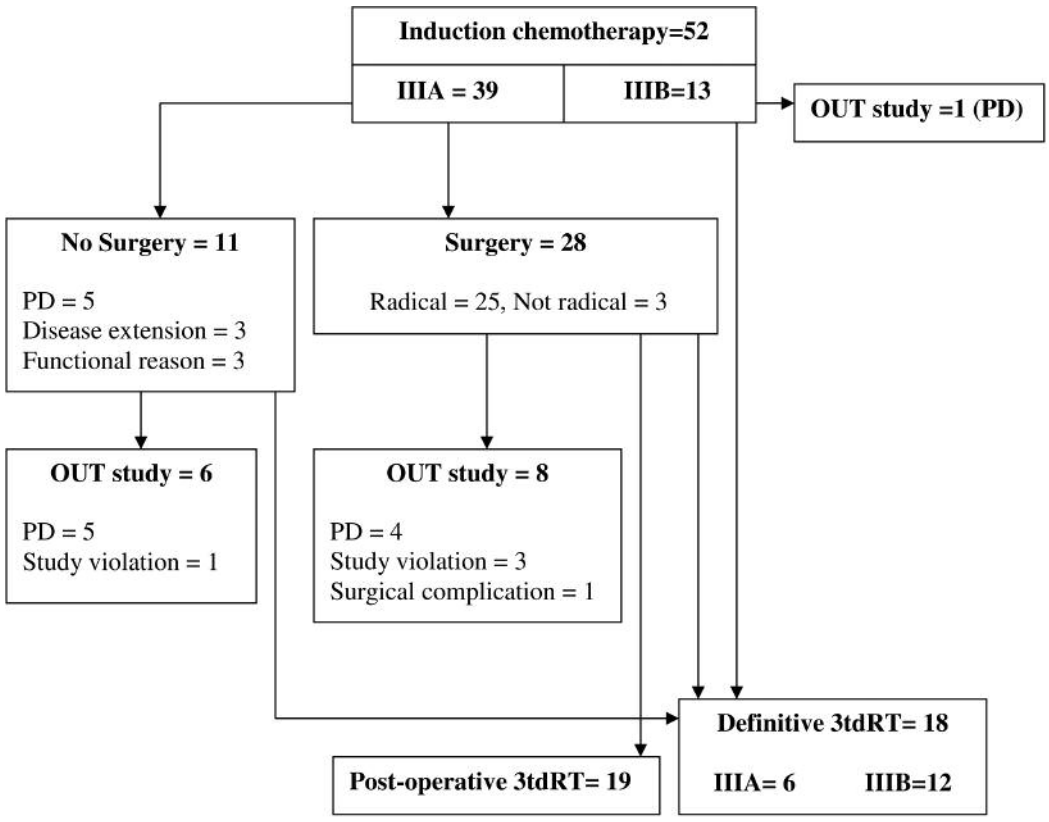

Figure 1. *Flow chart of study design and treated patients. 3tdRT, Three-times daily radiotherapy; PD, disease progression.*

Discussion

At the study planning, the present protocol represented, on the basis of our knowledge, one of the first experiences of platinum-based iCT with sequential 3tdRT in stage IIIA-B NSCLC. Since surgical resection represented the preferred local treatment, definitive 3tdRT was originally reserved only for the unresectable IIIA and IIIB pts; afterwards, IIIA resected pts were offered the most effective systemic option (platinum-based CT) and the most effective local treatment (post-op 3tdRT). As a consequence, this choice increased the population heterogeneity, reducing the statistical power of the study. Conscious of such a limitation, the results are reported not only for the whole population, but also on the basis of irradiation purpose (post-op and definitive 3tdRT).

Three main aspects emerged: satisfactory compliance with therapy, a higher incidence of systemic failures over locoregional progressions, especially in the resected pts, and a similar long-term outcome for the definitive 3tdRT and post-op irradiation treatments.

Compliance was much better than expected. Most of the pts completed the planned iCT and only 8% of pts stopped treatment before the last cycle, confirming the good regimen tolerance (25-29). In contrast to the literature (30), only 18% of the resected pts experienced severe perioperative morbidity, without any fatal event. A possible explanation may be the low number of pneumonectomies performed, since it has been reported that surgical extension is predictive of complications after iCT (31). As far as radiation-induced toxicity was concerned, all but one irradiated patient completed the 3tdRT with only 10.8% of severe esophagitis, well below reported data (8, 32). Although this finding could possibly be attributable to incidental favourable patient selection (21), the possible potential favourable impact of the treatment strategy itself on the observed tolerance should not be excluded, as similar findings of 10% of severe dysphagia in the Continuous Hyperfractionated Accelerated Radiation Therapy Week End Less (CHARTWEL) Trial have been reported (33). A substantial number of pts (15 out of 52, 29%) did not proceed to 3tdRT for various reasons, introducing a potential lack of feasibility of the study. Nevertheless, the discontinuations were mainly due to PD (10 pts) at various stages of the treatment (iCT start - 3tdRT end) and seemed mostly to reflect the natural history of the

Table II. *Patterns of progression for the whole population and stratified for treatment.*

	Total patients (n=52)	3tdRT patients (n=37)	IIIA Post-op 3tdRT patients (n=19)	IIIA-B Definitive 3tdRT patients (n=18)
Disease-free at last follow-up	7 (13.5%)	6 (16.2%)	3 (15.8%)	3 (16.7%)
PD	42 (80.7%)	29 (78.4%)	15 (78.9%)	14 (77.8%)
Local	14 (26.9%)	8 (21.6%)	2 (10.5%)	6 (33.3%)
Systemic	25 (48.1%)	18 (48.6%)	10 (52.6%)	8 (44.4%)
Both	2 (3.8%)	2 (5.4%)	2 (10.5%)	-
Unknown	1 (1.9%)	1 (2.7%)	1 (5.3%)	-
Unknown	3 (5.8%)	2 (5.4%)	1 (5.3%)	1 (5.5%)

3tdRT, three-times daily radiotherapy; Post-op, postoperative; PD, disease progression.

Table III. *Survival for the whole population and stratified for treatment.*

	Median OS (months)	2-Year OS	5-Year OS	*p-Value*
Total population (52 pts.)	15	40%	19%	-
Clinical stage (IIIA *vs.* IIIB)	19 *vs.* 13	44% *vs.* 26%	19% *vs.* 17%	0.78
Response to iCT (PR *vs.* SD)		46% *vs.* 25%	17% *vs.* 25%	0.32
Surgery *vs.* no surgery		45% *vs.* 33%	20% *vs.* 16%	0.50
IIIA after surgery (28 pts.)				
Radical *vs.* non-radical surgery		52% *vs.* 0%	23% *vs.* 0%	0.04
IIIA after radical surgery (25 pts.)				
N2 positive stations (≤2 *vs.* >2)		69% *vs.* 22%	31% *vs.* 11%	0.13
3tdRT patients (37 pts.)				
Postoperative *vs.* definitive 3tdRT	27 *vs.* 15	55% *vs.* 42%	25% *vs.* 21%	0.87

OS, Overall survival; iCT; induction chemotherapy; PR, partial response; SD, stable disease; 3tdRT, three-times daily radiotherapy.

disease rather than study compliance. Similar findings have been reported elsewhere, such as in the Cancer And Leukaemia Group B (CALGB) 8935 trial where, out of 74 enrolled pts, only 43 (58%) completed the planned scheduled treatment, due to overcoming PD, deaths or other reasons (34).

Although the overall rate of failures was similar in the post-op and definitive 3tdRT pts, the failure patterns reflected the local treatment performed. As expected, surgery by itself led to better local control, thus, in the post-op 3tdRT pts a higher incidence of metastases than local recurrences occurred (Table II). In constrast, in the definitive 3tdRT group the failures were more balanced, with only a slight prevalence of systemic spread over local PD. Kumar *et al.* reported on a similar trend (34). Overall, 70% of pts failed, but while the resected pts experienced predominantly distant spread, in the unresectable pts local relapses were more frequent. The metastases among the post-op pts might therefore reflect either possible iCT ineffectiveness in eradicating occult disease at the time of surgery, or the ability of resection plus post-op RT to increase local control, shifting the first failure to a distant site. In the unresectable disease, it was concluded that the results represented an indirect validation of the ability of non-surgical treatment to control bulky locoregional disease (17, 34, 35). Although the present findings did not differ consistently from the CALGB trial especially for the resected pts, the possible inadequacy of iCT in preventing metastatic spread from occult disease was unlikely, since the regimen has proved its effectiveness (25, 26, 28, 29); furthermore, the planned number of cycles is a common standard and evidence does not exist supporting a prolongation for more than three cycles. Positron tomography (PET) was not included in the planned staging as a routine procedure in the present study. Since the role of PET in the early diagnosis of NSCLC metastases is now established (36-38), it is likely that a consistent number of

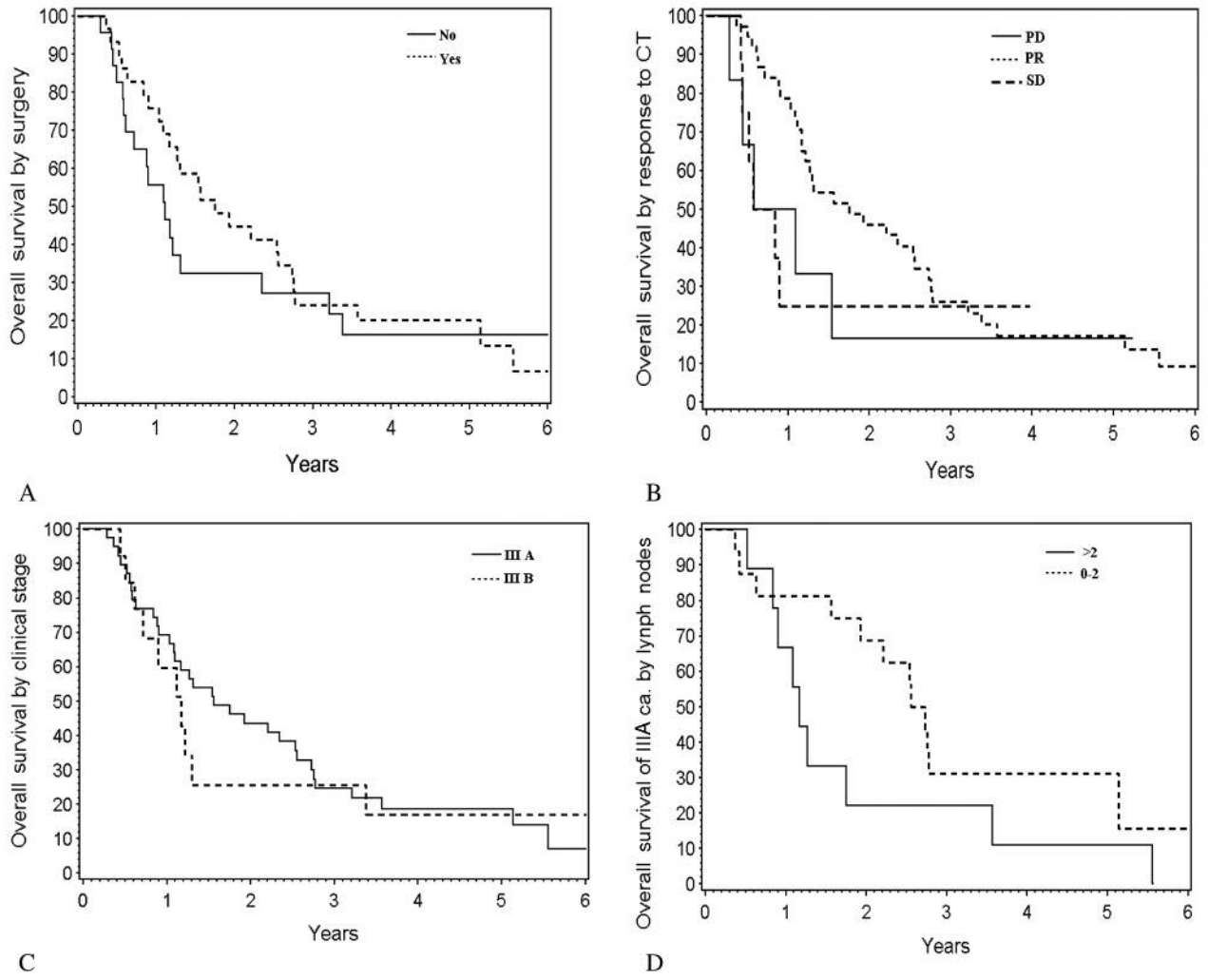

Figure 2. *Overall survival relative to surgery (A), response to induction chemotherapy (PD, disease progression; PR, partial response; SD, stable disease) (B), clinical stage (stage IIIA, stage IIIB) (C), and number of positive mediastinal lymph nodal stations at surgery (0-2, more than 2) (D).*

pts already had occult systemic disease at diagnosis, thus affecting the results, especially in the post-op pts, where local control was more likely to be achieved with resection.

Compared with others (17, 34, 39), a prevalence of local over systemic failures was not observed in the definitive 3tdRT pts, on the contrary, local PD did not outweigh metastases. Although the low number of pts did not allow definitive conclusions, slight 3tdRT effectiveness in local disease control might be hypothesized. As pointed out, the three pts actually alive in this group reached a complete response after irradiation and were still free of disease at the last follow-up. Within the statistical limitations it could be speculated that in a restricted group of stage III pts, when disease is still loco-regional, a more intensive local treatment might improve disease control and consequently outcome. The impact of local control on survival, has already been demonstrated in the study of Rojas *et al*. where 2-year OS was significantly affected by the achievement of primary tumor control (33).

As far OS was concerned, the present findings were comparable to other series (34). Although a short-term OS difference occurred between stage IIIA and IIIB, it was lost at longer follow-up. Similar results occurred in the restricted group of irradiated pts, where the 2-year difference between post-op and definitive 3tdRT pts was no longer observed after 5 years. Despite the lack of statistical significance, due to the low statistical power, a better outcome for definitive 3tdRT may be argued; on the other hand, it is also possible that this observation could be consequent on the sub-optimal result for the post-op pts. Both explanations are reasonable. Lorent *et al*. in a trimodality protocol for IIIA-N2 pts, reported a 5-year OS of 21% for the whole population, although post-op pts experienced a 5-year OS of 35% , slightly better than the present

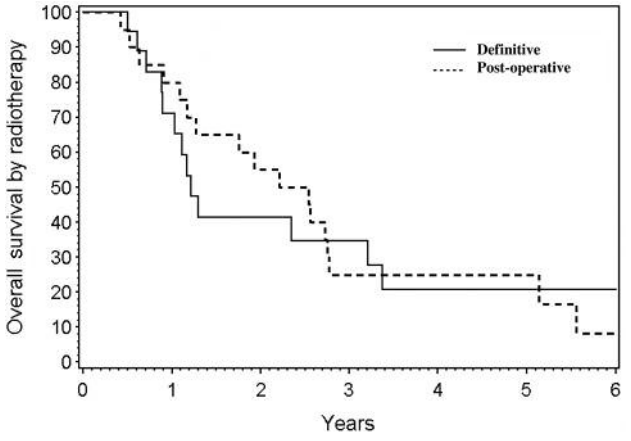

Figure 3. *Overall survival relative to purpose of three-times daily radiotherapy (post-operative 3tdRT vs. definitive 3tdRT).*

25% (40). Belani *et al*. reported on stage IIIA-B pts treated sequentially with iCT and definitive 3tdRT, observing a 2-year OS of 44% comparable to the present 42% (41). Finally, Hishikura *et al*. in a similar study for stage III pts, experienced a 2-year OS of 50%, but local failure was high (57%) compared to metastases (30%) and the authors underlined the importance of further local control improvement (42).

Conclusion

The reported treatment is feasible and well tolerated with good compliance and low toxicity. No significant outcome improvement of 3tdRT as post-op treatment occurred in stage IIIA pts, where local control was managed by surgery. 3tdRT as definitive treatment may have a role in selected pts; the potential candidates represent a very restricted group in which the disease, although locally advanced, is still locoregional, thus justifying a more intensive local approach.

Conflict of Interest Statement

No financial involvement or personal relationship with people or organizations that could inappropriately influence study results exist for any of the authors.

References

1 Slanina J and Laubenberger J: CT-based study on potential mediastinal lymph node spread of patients with lung cancer. Strahlenther Onkol *178*: 199-208, 2002.

2 Grunenwald DH and Albain KS: The potential role of surgery after induction treatment. Semin Radiat Oncol *14*: 335-339, 2004.

3 Rosell R, Gomez-Codina J, Camps C *et al*: Preresectional chemotherapy in stage IIIA non-small cell lung cancer: a 7-year assessment of a randomized trial. Lung Cancer *26*: 7-14, 1999.

4 Roth JA, Atkinson EN, Fossella F *et al*: Long-term follow-up of patients enrolled in a randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small cell lung cancer. Lung Cancer *21*: 1-6, 1998.

5 Rush VW: Surgery for stage III non-small cell lung cancer. Cancer Control *1*: 455-466, 1994.

6 Bollmann A, Blakenburg T, Haerting J *et al*: Survival of patients in clinical stages I-IIIb of non-small cell lung cancer treated with radiation therapy alone. Strahlenther Onkol *180*: 488-496, 2004.

7 Cox JD, Azarnia N, Byhardt RW *et al*: A randomized phase I/II trial of hyperfractionated radiation therapy with total dose of 60.0 Gy to 79.2 Gy: possible survival benefit with >69.6 Gy in favourable patients with RTOG stage III non-small cell lung carcinoma: report of Radiation Therapy Oncology Group 83-11. J Clin Oncol *8*: 1543-1555, 1990.

8 Saunders M, Dische S, Barrett A *et al*: Continuous hyperfractionated accelerated radiotherapy (CHART) *versus* conventional radiotherapy in non-small cell lung cancer: a randomised multicentre trial. Lancet *350*: 161-165, 1997.

9 Saunders M, Dische S, Barrett A *et al*: Continuous hyperfractionated accelerated radiotherapy (CHART) *versus* conventional radiotherapy in non-small cell lung cancer: mature data from the randomized multicentre trial. Radiother Oncol *52*: 137-148, 1999.

10 Curran WJ, Scott CB, Langer CJ *et al*: Long-term benefit is observed in a phase III comparison of sequential *vs*. concurrent chemo-radiation for patients with unresectable stage III NSCLC: RTOG 9410). Proc Am Soc Clin Oncol, J Clin Oncol *22*: (Abstract 2499), 2003.

11 Furuse K, Fukuoka M Kawahara M *et al*: Phase III study of concurrent *versus* sequential thoracic radiotherapy in combination with mitomycin, vindesine and cisplatin in unresectable stage III non-small cell lung cancer. J Clin Oncol *17*: 2692-2699, 1999.

12 Gagel B, Piroth M, Pinkawa M *et al*: Gemcitabine concurrent with thoracic radiotherapy after induction chemotherapy with gemcitabine/vinorelbine in locally advanced non-small cell lung cancer. Strahlenther Onkol 182: 263-269, 2006.

13 Choi H, La Porte K, Knill-Selby E *et al*: Esophagitis in combined modality therapy for locally advanced non-small cell lung cancer. Semin Radiat Oncol *9*: 90-96, 1999.

14 Semrau S, Bier A, Thierbach U *et al*: Concurrent radiochemotherapy with vinorelbine plus cisplatin or carboplatin in patients with locally advanced non-small cell lung cancer (NSCLC) and an increased risk of treatment complications. Strahlenther Onkol *179*: 823-831, 2003.

15 Semrau S. Bier A, Thierbach U *et al*: 6-Year experience of concurrent radiochemotherapy with vinorelbine plus a platinum compound in multimorbid or aged patients with inoperable non-small cell lung cancer. Strahlenther Onkol *183*: 30-35, 2007.

16 Werner-Wasik M, Pequignot E, Leeper D *et al*: Predictors of severe esophagitis include use of concurrent chemotherapy, but not the length of irradiated esophagus: a multivariate analysis of patients with lung cancer treated with non-operative therapy. Int J Radiat Oncol Biol Phys *48*: 689-696, 2000.

17 Dillman R, Seagren S, Propert K, *et al*: A randomized trial of induction chemotherapy plus high dose radiation *versus* radiation alone in stage III non-small cell lung cancer. N Engl J Med *323*: 940-945, 1990.

18 Dillman RO, Herndon J, Seagren SL *et al*: Improved survival in stage III non-small cell lung cancer: seven-year follow-up of Cancer and Leukaemia Group B (CALGB) 8433 trial. J Natl Cancer Inst *88*: 1210-1214, 1996.
19 Le Chevalier T, Arriagada R, Quoix E *et al*: Radiotherapy alone *versus* combined chemotherapy and radiotherapy in non resectable non-small cell lung cancer. Lung Cancer *10*: S239-S244, 1994.
20 Sause WT, Scott C, Taylor S *et al*: Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small cell lung cancer. J Natl Cancer Inst *87*: 198-205, 1995.
21 Catalano G, Jereczek-Fossa BA, De Pas T *et al*: Three-time daily radiotherapy with induction chemotherapy in locally advanced non-small cell lung cancer: feasibility and toxicity study. Strahlenther Onkol *181*: 363-371, 2005.
22 World Health Organization. WHO Handbook for Reporting Results of Cancer Treatment. WHO Offset Publication No. 48. Geneva, Switzerland, World Health Organisation, 1979.
23 Fowler JF: The linear quadratic formula and progress in fractionated radiotherapy. Br J Radiol *62*: 679-694, 1989.
24 International Commission on Radiation Units and Measurements (ICRU) Report 50. Prescribing, Recording and Reporting Photon Beam Therapy. ICRU, 1993.
25 Cardenal F, Paz López-Cabrerizo M, Antón A, *et al*: Randomized phase III study of gemcitabine-cisplatin *versus* etoposide-cisplatin in the treatment of locally advanced or metastatic non-small cell lung cancer. J Clin Oncol *17*: 12-18, 1999.
26 Crinò L, Conte P, De Marinis F *et al*: A randomized trial of gemcitabine cisplatin *versus* mitomycin, ifosfamide and cisplatin (MIC) in advanced non-small cell lung cancer (NSCLC): A multicenter phase III study. J Clin Oncol *17*: 3522-3530, 1999.
27 De Pas T, Catalano G, Pastorino U *et al*: Very low acute toxicity of three fractions per day accelerated radiotherapy given after induction chemotherapy and surgery in stage III non-small cell lung cancer. Lung Cancer *30*: 149-150, 2000.
28 Rinaldi M, Crinò L, Scagliotti G *et al*: A three-week schedule of gemcitabine-cisplatin in advanced non-small cell lung cancer with two different cisplatin dose levels: a phase II randomized trial. Ann Oncol *1*: 1295-1300, 2000.
29 Van Zandwijk N, Smit EF, Kramer GW *et al*: Gemcitabine and cisplatin as induction regimen for patients with biopsy-proven stage IIIA N2 non-small cell lung cancer: a phase II study of the European Organization for Research and Treatment of Cancer, Lung Cancer Cooperative Group (EORTC 08955). J Clin Oncol *18*: 2658-2664, 2000.
30 Roberts JR, Eustis C, Devore R *et al*: Induction chemotherapy increases perioperative complications in patients undergoing resection for non-small cell lung cancer. Ann Thorac Surg *72*: 885-888, 2001.
31 Leo F, Solli PG, Veronesi G *et al*: Does chemotherapy increase the risk of respiratory complications after pneumonectomy? J Thorac Cardiovasc Surg *132*: 519-523, 2006.
32 Metha MP, Tannehill SP, Adak S *et al*: Phase II trials of hyperfractionated accelerated radiation therapy for nonresectable non-small cell lung cancer: results of Eastern Cooperative Oncology Group 4593. J Clin Oncol *16*: 3518-3523, 1998.
33 Rojas AM, Lyn BE, Wilson EM *et al*: Toxicity and outcome of a Phase II Trial of taxane-based neoadjuvant chemotherapy and 3-dimensional, conformal, accelerated radiotherapy in locally advanced non-small cell lung cancer. Cancer *107*: 1321-1330, 2006.
34 Kumar P, Herndon J, Langer M *et al*: patterns of disease failure after trimodality therapy of non-small cell lung carcinoma pathologic stage IIIA (N2). Analysis of Cancer and Leukaemia Group B Protocol 8935. Cancer *77*: 2393-2399, 1996.
35 Elias A, Skarin A, Gonin R *et al*: Neoadjuvant treatment of stage IIIA non-small cell lung cancer. Am J Clin Oncol *17*: 26-36, 1994.
36 Dizendorf EV, Baumert BG, von Schultess GK *et al*: Impact of whole-body ^{18}F-FDG PET on staging and managing patients for radiation therapy. J Nucl Med *44*: 24-29, 2003.
37 Nestle U, Walter K, Schimdt S *et al*: ^{18}F-deoxyglucose positron emission tomography (FDG-PET) for the planning of radiotherapy in lung cancer: high impact in patients with atelectasis. Int J Radiat Oncol Biol Phys *44*: 593-597, 1999.
38 Paulsen F, Scheiderbauer J, Eschmann SM *et al*: First experiences of radiation treatment planning with PET/CT. Strahlenther Onkol *182*: 369-375, 2006.
39 Le Chevalier T, Arriagada R, Quoix E *et al*: Radiotherapy alone *versus* combined chemotherapy and radiotherapy in non resectable non-small cell lung cancer: first analysis of a randomized trial in 353 patients. J Natl Cancer Inst *83*: 417-423, 1991.
40 Lorent N, De Leyn P, Lievens Y *et al*: Long-term survival of surgically staged IIIA-N2 non-small cell lung cancer treated with surgical combined modality approach: analysis of a 7-year prospective experience. Ann Oncol *15*: 1645-1653, 2004.
41 Belani CP, Wang W, Johnson DH *et al*: Phase III study of Eastern Cooperative Oncology Group (ECOG 2597): induction chemotherapy followed by either standard thoracic radiotherapy or hyperfractionated accelerated radiotherapy for patients with unresectable stage IIIA and B non-small cell lung cancer. J Clin Oncol *23*: 3760-3767, 2005.
42 Hishikura SI, Ohe Y, Nihei K *et al*: A phase II study of hyperfractionated accelerated radiotherapy (HERT) after induction cisplatin (CDDP) and vinorelbine (VNR) for stage III non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys *61*: 1117-1122, 2005.

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