EUR. J. ONCOL., vol. 18, n. 1, pp. 5-13, 2013

Chemoradiation for stage III non-small cell lung cancer

Sara Ramella, Michele Fiore, Aurelia Iurato, Luca E. Trodella, Lucio Trodella, Rolando M. D'Angelillo

Radioterapia Oncologica, Università Campus Bio-Medico di Roma, Italia

Summary. Approximately one third of patients with non-small cell lung cancer (NSCLC) have locally advanced disease (stage III) and a few patients may benefit from surgical treatment exclusively. For this reason, the treatment of stage III NSCLC will require a combination of the three oncological disciplines: Cancer Surgery, Radiation Oncology and Clinical Oncology. The choice of treatment is guided by the presentation of the disease, indeed the patient is classified with locally advanced disease either for involvement of mediastinal structures (T3-T4) or for lymph node involvement showed at histological examination (pN2) or preoperative exams (cN2-N3). Therapeutic scenarios that we can observe are therefore an adjuvant treatment in patients who have an increased risk of local recurrence (pN2), a neoadjuvant treatment in patients with potentially resectable or borderline (cN2), and in patients with inoperable disease for bulky disease or contralateral lymph nodes (cN3) that need a radical treatment of radiochemotherapy. The multimodal approach is currently considered the best strategy but the timing needed to integrate the different disciplines and the use of various drugs in the combined treatment still has an incomplete classification. Recent studies and meta-analysis have tried to give an answer to these questions. Our aim is to present the latest data from the literature on different multimodal approach.

Key words: NSCLC, locally advanced disease, radiochemotherapy, adjuvant, neoadjuvant

«LA RADIOCHEMIOTERAPIA PER IL CARCINOMA POLMONARE NON A PICCOLE CELLULE STADIO III»

Riassunto. Circa un terzo dei pazienti con carcinoma polmonare non a piccole cellule (NSCLC) ha una malattia localmente avanzata (stadio III) e pochi pazienti possono beneficiare di un trattamento chirugico esclusivo. Per questa ragione il trattamento del NSCLC stadio III prevede la combinazione delle tre discipline oncologiche: Chirugia Oncologica, Radioterapia Oncologica ed Oncologia Clinica. La scelta del trattamento è guidata anche dalla presentazione di malattia, infatti il paziente è classificato con malattia localmente avanzata o per coinvolgimento delle strutture mediastiniche (T3-T4) o per coinvolgimento linfonodale evidenziato all'esame istologico (pN2) o già presente agli esami preoperatori (cN2-N3). Gli scenari terapeutici che possiamo osservare sono quindi un trattamento adiuvante nei pazienti che presentano un aumentato rischio di recidiva locale (pN2), un trattamento neoadiuvante nei pazienti con malattia potenzialmente resecabile o borderline (cN2) ed infine i pazienti con malattia inoperabile o per malattia bulky o per linfonodi controlaterali (cN3) che necessitano di un trattamento radicale di radiochemioterapia. L'approccio multimodale attualmente è ritenuto la migliore strategia terapeutica ma ancora presenta una non completa classificazione sia nel timing con il quale devono integrarsi le diverse discipline sia nell'utilizzo dei farmaci da impiegare nel trattamento combinato. Recenti studi e meta-analisi hanno provato a dare una risposta a queste domande. Il nostro scopo è di presentare gli ultimi dati di letteratura sui differenti approcci multimodali.

Parole chiave: NSCLC, malattia localmente avanzata, radiochemioterapia, adiuvante, neoadiuvante

Introduction

Probably stage III NSCLC disease is the most significant scenario for integrating strategies. In fact, each oncologic arm such as radiation therapy, surgery and chemotherapy play a role in the combined approach to achieve the better results. Stage III is a large spectrum of disease presentation that includes patients with mediastinal nodes discovered only on histologic examination (pN2) and patients with large mediastinal lymph nodes or contralateral disease (cN2-N3). The lack of homogeneity has produced many treatment options, but generally within multimodality approach such as adjuvant, neoadjuvant and definitive chemoradiation. In the following sections the most recent literature data regarding these approaches will be presented.

The recent years have seen significant gains in the understanding of NSCLC biology and growth factors signalling with the development of target therapies. Significant advances have also be made in radiation dosimetric planning, tumour imaging and treatment delivery techniques that allow to assess and account for uncertainties. So, as Rengan (1) said: "The pendulum is beginning to swing".

Adjuvant radiotherapy in pN2 patients

In the management of completely resected patients, the role of adjuvant radiotherapy in the past decade has been controversial. After the PORT publication in 1998 (2), prescription of adjuvant radiotherapy underwent an important contraction (3) because of the detrimental effect shown. In fact, local recurrences were diminished in PORT group but patients deaths were increased for pulmonary and cardiac toxicity. Since then a great literature debate is emerged underling several critical points of trials included PORT meta-analysis such as recruitment, dose and fractionation, volume, technique and technology (4-6). The most important observations could be summarized in the following ones:

- Stratification before randomization is necessary to ensure equal distribution of known prognostic factors. No mention was made of pre-operative weight loss, type of surgery or pulmonary function.

- Other faults of the meta-analysis include large proportions of ineligible patients, inappropriate staging, and a lack of quality control programmes.

- The main criticism of the PORT analysis is the failure of investigators to consider the way in which the radiotherapy was given.

In 2005 an update of PORT of meta-analysis including two new trials was published. While at the time of original publication, there was no difference in outcome between the groups according to radiotherapy technique used [Co60 vs Linac] (p=0.153), in the new analysis the interaction borders statistical significance (p=0.052) (7), underlying the importance of radiotherapy delivering.

The role of adjuvant radiotherapy is postulated on the literature data which report crude local-regional failure rates (LRFs) of 6 to 65% for N2 disease (8-9). Improving locoregional control, one would suspect that outcomes for patients with lung cancer might be improved.

Several interesting trials about this topic have been published in 2010. Saynak (10) reported a review discussing the rationale, the interaction between PORT and adjuvant chemotherapy but most importantly target volumes and technique. These peculiar aspects of radiotherapy planning have been also investigated by The Lung Adjuvant Radiotherapy Trial Investigators Group (11) which has recently reported variations in target volume definition in stage III disease. Results have shown significant inter-clinicians variations, so mandatory quality procedures have been incorporated into the current Lung ART study, an ongoing study which is testing the role of PORT in pN2 disease.

In the Italian Survey on Lung Cancer Radiotherapy (12), 98.5% of responding institutions prescribed radiotherapy (RT) in pN2 disease revealing the knowledge of the high percentage of local relapse in this group of patients. In 2010 an experience from Florence University (13) confirmed in 175-N2 resected patients the significant reduction in local recurrence with PORT (15.1% vs 32.1% respectively). The role of radiotherapy on local recurrence free-survival was confirmed both at univariate (HR:0.45; 0.24-0.88) and multivariate analysis (HR:0.37;0.17-0.79) with acceptable toxicity. Another postoperative

paper published in *International Journal of Radiation Therapy, Oncology, Biology and Physics* by Zou and colleagues, underlined the role of postoperative radiotherapy in 183- pN2 patients (14). The 5-year overall survival rate was 30.5% in the post operative chemoradiation group, and 14.4% in the post operative chemotherapy group (p=0.007). As compared with chemotherapy alone, adjuvant treatment with both radiotherapy and chemotherapy improves survival in patients with completely resected Stage III–N2 nodal disease in NSCLC (14).

At the end of a 2010 meta-analysis (15) investigating adjuvant chemotherapy authors concluded that "randomised trials are needed to assess whether modern radiotherapy is effective as an adjuvant treatment." All the radiotherapists should be encouraged to propose research in this emerging area of interest.

Neoadjuvant approach in cN2 patients

Trimodality therapy (radiation, chemotherapy and surgery) has been investigated in two famous randomized trials. INT 1039 published by Albain (16) compared concurrent radiochemotherapy followed by surgery to definitive chemoradiation in stage IIIA patients. Progression-free survival was significantly improved for patients who underwent surgery (13 vs 10.5 months), but there were no significant differences in 5-year overall survival rates (27% vs 20%). An exploratory hypothesis- generating analysis of this trial suggested that patients undergoing pneumonectomy poorly fared when compared with the matched cohort of chemoradiotherapy patients and patients who underwent a lobectomy may fare better than those treated with concurrent chemoradiotherapy.

A recent phase III trial also compared the benefit of surgery or radiation therapy after induction chemotherapy for stage IIIA NSCLC patients. The European Organization for the Research and Treatment of Cancer (EORTC) carried out a trial in which patients received 3 cycles of platinum-based chemotherapy followed by randomization to either surgery or 60 Gy of thoracic radiation (17). No difference in median, progression free, or overall survival outcome between the 2 arms was observed.

Even if these phase III trials failed to show a survival benefit to surgery in the management of N2 patients, several observations arise from literature regarding type of surgery (pneumonectomy vs lobectomy), radiotherapy technique and patients selection. However, in both trials local tumor progression was approximately reduced by 50% by the addiction of surgery (18) so intervention remains an attractive treatment option.

Nodal clearance (i.e., the complete pathologic disappearance of any sign of tumor at the nodal level) and, therefore, the pathologic downstaging to stage 0 to I, are generally shared as a surrogate end points for the assessment of the efficacy of any inductive protocol (19-20). Neoadjuvant chemotherapy may achieve a pathologic mediastinal downstaging from N2 to N1-0 disease in 61% of patients. Instead, a complete tumor and nodal pathologic response rate (i.e., a complete disappearance of the primitive tumor and its nodal metastases) is reported to be in the range of 5 to 10%, with a 60% local recurrence rate after surgery (21).

Neoadjuvant chemoradiation delivered with a combination of cisplatin and etoposide (which is the old standard association) in selected patients offers a nodal clearance of 37% with a pCR ranging from 14 to 17% (22-24). A retrospective study published by Higgins and colleagues (25) showed a mediastinal pathological complete response (pCR) of 35% after preoperative chemotherapy versus 65% after preoperative chemoradiation (p=0.01). On multivariate analysis a mediastinal pCR was associated with improved disease free survival (DFS) and local control (LC) but not overall survival (OS).

More recently, some third generation compounds have been added to cisplatin or carboplatin to improve these results. Different trials explored the adding of taxanes to radiotherapy and platinum compounds, but the reported results are generally poor with a pCR ranging from 3.8 to 11% with both paclitaxel or docetaxel (26-29).

Gemcitabine (2-2'-difluorodeoxycytidine) is a well known cytotoxic drug and a potent radioenhancer. *In vitro*, the radiosensitization is dose and time dependent, also at a noncytotoxic concentration, and it is greatest when exposure to drug precedes radiation. Its radiosensitization activity has been correlated with the

ability to deplete dATP pools through the inhibition of the ribonucleotide reductase by the difluoro-deoxycytidine diphosphate (30). Adding a full dose of cisplatin to weekly gemcitabine in the neoadjuvant setting, results in a pathologic CR rate of around 30% with a nodal clearance in 50% of patients (31).

Nowadays, in a metastatic setting, chemotherapy compounds are generally given according to tumor histology (32) with pemetrexed as an active drug in non-squamous histology vs gemcitabine as more effective in squamous one's.

Both drugs have a radioenhancer effect (30, 33) and could be concurrently administered with radiation (34, 35).

Actually few data are available according to this issue and generally refer to retrospective analysis (36).

Therefore in locally advanced non-small cell lung cancer (LA-NSCLC), neoadjuvant setting is the best way to explore personalised treatment strategy: radiotherapy is per se an individualised treatment for tumor location, dose-constraint to organ at risk and planning solutions (Figure 1); chemotherapy will be adopted according to tumor histology and surgery proposed to those patients where a lobectomy or bilobectomy could be performed. Moreover the ability to have an immediate surrogate end-point such as nodal clearance could allow verifying testing hypothesis in a little time.

Definitive radiochemotherapy in Stage IIIA and IIIB disease

In locally-advanced unresectable NSCLC standard treatment is chemoradiation and concurrent modality offers the best results. Two new articles confirm this hypothesis. At JCO May 2010 Auperin

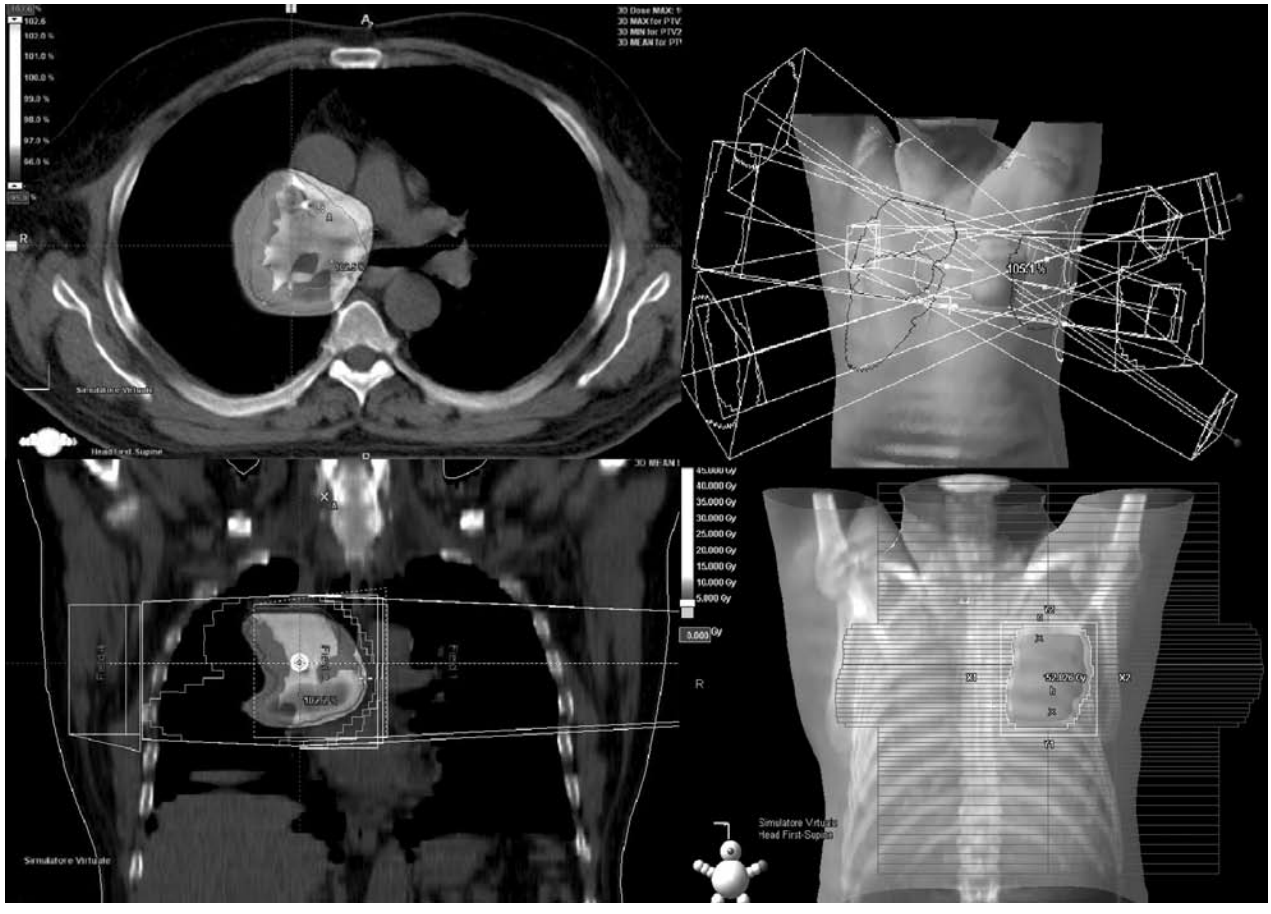

Figure 1. 3-Dimensional Conformal Radiotherapy: an example of dose distribution and treatment planning

at al (37) reported a new meta-analysis which undertook systematic searches for trials, followed by central collection, checking, and reanalysis of updated individual patient data (1205 patients). Concomitant radiochemotherapy, as compared with sequential radiochemotherapy, improved survival of patients with locally advanced NSCLC, primarily because of a better locoregional control. A significant benefit of concomitant radiochemotherapy on overall survival (HR, 0.84; 95% CI, 0.74 to 0.95; p = 0.004), with an absolute benefit of 5.7% (from 18.1% to 23.8%) at 3 years and 4.5% at 5 years is observed. Concomitant treatment decreased locoregional progression (HR, 0.77; 95% CI, 0.62 to 0.95; p = 0.01); its effect was not different from that of sequential treatment on distant progression (HR, 1.04; 95% CI, 0.86 to 1.25; p = 0.69). The benefit was also confirmed in elderly patients (more than 70 years) with good performance status.

In January 2010 Cochrane Lung Cancer Group (38) published an update of the reviews in 2004 incorporating additional trials and more mature data. It demonstrates the benefit of concurrent chemoradiation over sequential treatment with a 10% absolute survival benefit at 2 years (HR 0.74, 95% CI 0.62 to 0.89). Authors underlined that patient selection is an important consideration in view of the added toxicity of concurrent treatment. Uncertainty remains as to how far this is purely due to a radiosensitising effect and whether similar benefits could be achieved by using modern radiotherapy techniques and more dose intensive accelerated and/ or hyperfractionated radiotherapy regimens.

In 2011, Curran (39) reported the updated results of RTOG 9410 39 comparing sequential arm with concurrent and concurrent/hyperfractionated ones: six hundred and one patients were randomized and survival data at 11 years was reported. Concurrent arm obtained the better survival in comparison with both sequential and concurrent/hyperfractionated arm. Another confirmation of no benefit of altered fractionation is the CHARTWEL trial (40) in which no significant survival benefit is reported.

Even if concomitant treatment is considered the gold standard (41), the question of which drug is the best solution for concurrent radiochemotherapy is still open. Two phase III trials have been published in 2010 testing third generation drugs versus older regimens. Yamamoto and colleagues (42) reported that weekly paclitaxel and carboplatin plus TRT 60 Gy, (followed by two courses of paclitaxel and carboplatin) was equally efficacious and exhibited a more favorable toxicity profile than weekly irinotecan and carboplatin or mitomycin, vindesine and cisplatin.

Segawa *et al* (43) tested docetaxel and cisplatin versus mitomycin, vindesine, and cisplatin concurrently to radiotherapy. The first arm showed a better overall survival, a trend toward improved response rate, 2-year survival rate, median progression-free time, and median survival even if G3-4 esophagitis was likely to be more common in this group.

As previously reported, the role of histology in drug selection is an actual issue and a phase III trial are testing this hypotesis (PROCLAIM Trial). Nowadays, the debate around the role of induction and consolidation chemotherapy is not closed. Both solutions demonstrated no survival improvement in comparison with concurrent radiochemotherapy (44-46). However, induction chemotherapy to chemoradiation (with a maximum of 2-3 cycles) shows theoretical advantages such as: 1) decrease in tumor volume; 2) decrease in irradiated volume and 3) identification of a good prognostic group before chemoradiation. So, it could be an useful approach in order to reduce target volume and consequently reducing toxicity and escalating radiotherapy dosage (Figure 2).

The generally accepted standard radiation prescription dose has remained at the same level (60–63 Gy) for more than 30 years (47). Doses in this range provide inadequate local control (48). Results from studies of stereotactic radiation therapy for lung cancer estimate that biologically equivalent doses of 100 Gy are needed to achieve local control for the small-volume stage I lung cancers treated with that technique (49). In stage III disease, RTOG 9311 employed 3DCRT to safely escalate a fractionated radiation dose to 83.8 Gy in patients who did not receive concurrent chemotherapy (50). The RTOG 0117 reported the feasibility of escalated total dose (74Gy) with concurrent chemotherapy (Carboplatin AUC2 and Taxol 50 mg/mq/weekly) (51). This result confirm data of previous papers such as NCCTG 0028 (52) and CALGB 30105 (53). In both of them the

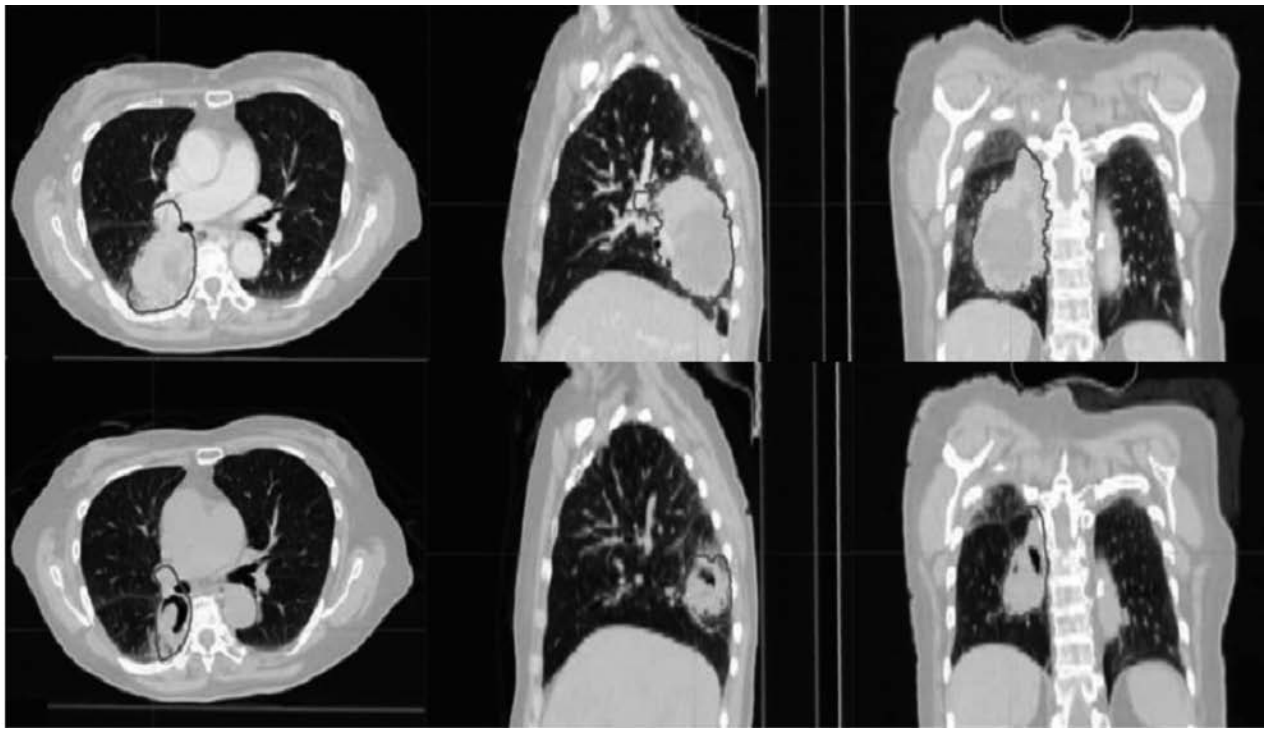

Figure 2. Reduced target volumes after two cycles of induction chemotherapy before chemoradiation

maximum tolerated dose (MTD) was determined to be 74 Gy with concurrent carboplatin and taxol at the same dose employed by RTOG 0117. In *Journal of Clinical Oncology* authors reported the phase II results. The median overall survival (OS) and progression-free survival (PFS) times for stage III patients were 21.6 months and 10.8 months, respectively. OS and PFS rates at 12 months were 72.7% and 50.0%, respectively. Twelve patients experienced grade 3 lung toxicity (two patients had grade 5 lung toxicity) (54). These encouraging results served as projection expectations for the high-dose radiation arms of the current RTOG 0617, which is a phase III intergroup trial (RTOG 0617/ NCCTG N0628/ CALGB 30609) testing 74 Gy vs 60 Gy with concurrent chemotherapy for patients with inoperable stage III NSCLC. Surprisingly, at ATRO 2011 results of inferiority of the experimental arm were reported and in the next months several hypothesis and explanations are expected.

A different approach has been proposed by Maastricht University Medical Center which published in *Journal of Clinical Oncology* on March 2010 an interesting paper without an unique total dose for all patients but with the concept of "escalate the dose that can be delivered to the tumor at an acceptable normal tissue complication" (55). Generally, patients with NSCLC receive a predefined radiation dose that is the same for all patients with a certain tumor stage. In this paper, the authors concluded that individualized prescribed radical radiotherapy based on normal tissue constraints with sequential chemoradiation shows survival rates that come close to results of concurrent chemoradiation schedules, with acceptable acute and late toxicity. In the era of tailored therapies, these results may be the basis for proposing an individualized approach also in radiotherapy delivering.

Conclusions

In conclusion, we would like to report results of an Italian Survey on pattern of care in NSCLC (RESPIRO project) (56). Contrary to literature data, sequential treatment in locally advanced disease is a

very common approach with more than 40% of Italian radiotherapy institutions declaring that they avoid concomitant therapies. Possible explanations for these differences may be related to organizational problems which could be overlapped by a creation of a multidisciplinary team. It is less clear if these differences indicate a lack of wide acceptance of the results of clinical trials preventing their implementation in the current clinical practice. However, the modern available technology and the knowledge in the management of integrated therapies side effects should improve application of standard treatment. In this setting, it could be postulated that an urgent need of collaborative groups with the others societies involved in the treatment of NSCLC is shown to offer the best therapy to our patients.

References

1. Rengan R, Hahn SM. Introduction: Non –Small- Cell Lung Cancer and Pleural Malignancies: the end of the era of therapeutic nihilism? Seminars in Radiation Oncology 2010; 20 (3): 147-8.
2. PORT Meta-analysis Trialists Group. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomized controlled trials. Lancet 1998; 352: 257-63.
3. Lally BE, Zelterman D, Colasanto JM, *et al*. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. J Clin Oncol 2006; 24 (19): 2998-3006.
4. Munro AJ. What now for postoperative radiotherapy for lung cancer? Lancet 1998; 25; 352(9124): 250-1.
5. Bonner JA, Spencer SA. Postoperative radiotherapy in non-small-cell lung cancer warrants further exploration in the era of adjuvant chemotherapy and conformal radiotherapy. J Clin Oncol 2006; 24 (19): 2978-80.
6. Granone P, Keller S, Trodella L, *et al*. Postoperative radiotherapy in completely resected, early-stage, non-small-cell lung cancer: reflections and future directions. Lancet Oncol 2002; 3 (10): 589-90.
7. Burdett S, Stewart L. PORT Meta-analysis Group. Postoperative radiotherapy in non-small-cell lung cancer: update of an individual patient data meta-analysis. Lung Cancer 2005; 47 (1): 81-3.
8. Kelsey CR, Marks LB, Hollis D, *et al*. Local recurrence after surgery for early stage lung cancer: An 11-year experience with 975 patients. Cancer 2000; 115: 5218-27.
9. Saynak M, Veeramachaneni NK, Hubbs JL, *et al*. Local failure after Complete resection of "Early-Stage" non-small cell lung cancer: The potential role of post-operative radiation therapy. Poster presentation at the 51st Annual Meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO), November 1-5, 2009, Chicago, IL.
10. Saynak M, Higginson D, Morris D, *et al*. Current status of postoperative radiation for non–small-cell lung cancer Semin Radiat Oncol 2010; 20: 192-200.
11. Spoelstra FO, Senan S, Le Péchoux C, *et al*. Lung Adjuvant Radiotherapy Trial Investigators Group. Variations in target volume definition for postoperative radiotherapy in stage III non-small-cell lung cancer: analysis of an international contouring study. Int J Radiat Oncol Biol Phys 2010; 76 (4): 1106-13.
12. Italian Survey on Lung Cancer Radiotherapy; http://www.radioterapiaitalia.it/cont__95.phtml
13. Scotti V, Meattini I, Saieva C, *et al*. Post-operative radiotherapy in N2 non-small cell lung cancer: a retrospective analysis of 175 patients. Radiother Oncol 2010; 96 (1): 84-8.
14. Zou B, Xu Y, Li T, *et al*. A multicenter retrospective analysis of survival outcome following postoperative chemoradiotherapy in non–small-cell lung cancer patients with N2 Nodal disease. Int. J Radiation Oncology Biol Phys 2010; 77: 321-8.
15. NSCLC Meta-analyses Collaborative Group. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet 2010; 375 (9722): 1267-77.
16. Albain KS, Swann RS, Rusch VW, *et al*. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: A phase III randomised controlled trial. Lancet 2009; 1: 379-86.
17. Van Meerbeeck JP, KramerGWP, Van Schil PEY, *et al*. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIa non-small cell lung cancer. J Natl Cancer Inst 2007; 99: 442-50.
18. De Ruysscher D, Dehing C, Bentzen SM, *et al*. Can we optimize chemo-radiation and surgery in locally advanced stage III non-small cell lung cancer based on evidence from randomized clinical trials? A hypothesis-generating study. Radiother Oncol 2009; 93: 389-95.
19. Betticher DC, Hsu Schmitz SF, Tötsch M, *et al.* Mediastinal lymph node clearance after docetaxel-cisplatin neoadjuvant chemotherapy is prognostic of survival in patients with stage IIIA pN2 non-small-cell lung cancer: a multicenter phase II trial. J Clin Oncol 2003; 21 (9): 1752-9.
20. Trodella L, Granone P, Valente S, *et al.* Neoadjuvant concurrent radiochemotherapy in locally advanced (IIIA-IIIB) non-small-cell lung cancer: long-term results according to downstaging. Ann Oncol 2004; 15 (3): 389-98.
21. Betticher DC, Hsu Schmitz SF, Tötsch M, *et al.* Prognostic factors affecting long-term outcomes in patients with resected stage IIIA pN2 non-small-cell lung cancer: 5-year follow-up of a phase II study. Br J Cancer 2006; 94 (8): 1099-106.

22. Albain KS, Rusch VW, Crowley JJ, *et al.* Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. J Clin Oncol 1995; 13 (8): 1880-92.
23. Albain KS, Crowley JJ, Turrisi AT 3rd, *et al.* Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: a Southwest Oncology Group phase II study, SWOG 9019. J Clin Oncol 2002; 20 (16): 3454-60.
24. Grunenwald DH, Andre F, Le Pechoux C, *et al.* Benefit of surgery after Chemoradiotherapy in stage IIIB (T4 and/or N3) non-small cell lung cancer. J Thorac Cardiovasc Surg 2001; 122: 796-802.
25. Higgins K, Chino JP, Marks L *et al*. Preoperative chemotherapy versus preoperative chemoradiotherapy for stage III (N2) NSCLC. Int J Radiation Oncology Biol Phys 2009; 75 (5): 1462-7.
26. Park BB, Park JO, Kim H, *et al.* Is trimodality approach better then bimodality in stage IIIA, N2 positive non-small cell lung cancer? Lung Cancer 2006; 53 (3): 323-30.
27. Kuten A, Anacak Y, Abdah-Bortnyak R, *et al.* Neoadjuvant radiotherapy concurrent with weekly paclitaxel and carboplatin and followed by surgery in locally advanced non-small-cell lung cancer. Am J Clin Oncol 2003; 26 (2): 184-7.
28. Wirth LJ, Lucca J, Ostler P, *et al.* Induction docetaxel and carboplatin followed by weekly docetaxel and carboplatin with concurrent radiotherapy, then surgery in stage III non-small cell lung cancer: a Phase I study. Clin Cancer Res 2003; 9 (5): 1698-704.
29. Maas KW, Phernambucq EC, Sharouni SY, *et al.* A phase II study of weekly docetaxel/cisplatin and concurrent radiotherapy followed by surgery in patients with stage III non-small cell lung cancer (NSCLC). J Clin Oncol, 2007 ASCO Annual Meeting Proceedings. 25, 18S, 2005: 18050 (abs).
30. Shewach DS, Hahn TM, Chang E, *et al*. Metabolism of 2,2'-difluoro-2'-deoxycytidine and radiation sensitization of human colon carcinoma cells. Cancer Res 1994; 15: 3218-23.
31. D'Angelillo RM, Trodella L, Ciresa M, *et al*. Multimodality treatment of stage III non-small cell lung cancer: analysis of a phase II trial using preoperative cisplatin and gemcitabine with concurrent radiotherapy. J Thorac Oncol 2009; 4 (12): 1517-23.
32. Scagliotti GV, Parikh P, von Pawel J, *et al.* Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008; 26 (21): 3543-51.
33. Bischof M, Weber KJ, Blatter J, *et al.* Interaction of pemetrexed disodium (ALIMTA, multitargeted antifolate) and irradiation in vitro. Int J Radiat Oncol Biol Phys 2002; 52 (5): 1381-8.
34. Trodella L, Granone P, Valente S, *et al.* Phase I trial of weekly gemcitabine and concurrent radiotherapy in patients with inoperable non-small-cell lung cancer. J Clin Oncol 2002; 20 (3): 804-10.
35. Seiwert TY, Connell PP, Mauer AM, *et al*. A phase I study of pemetrexed, carboplatin, and concurrent radiotherapy in patients with locally advanced or metastatic non-small cell lung or esophageal cancer. Clin Cancer Res 2007; 13 (2 Pt 1): 515-22.
36. Ramella S, D'Angelillo MR, Cellini F, *et al.* Radiochemotherapy for locally advanced NSCLC: which is the best association? From chemotherapy to biological target in 5 phases II trials. Radiother Oncol 2011; 99 (S1): s110, abs #279.
37. Auperin A, *et al*. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non–small-cell lung cancer. J Clin Oncol 2010; 28: 2181-90.
38. O'Rourke N, Roqué I, Figuls M, *et al*. Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database Syst Rev 2010; 16; 6.
39. Curran WJ Jr, Paulus R, Langer CJ, *et al*. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst 2011; 103 (19): 1452-60.
40. Baumann M, Herrmann T, Koch R, *et al*. Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC). Radiother Oncol 2011; 100 (1): 76-85.
41. Crinò L, Weder W, van Meerbeeck J, *et al*. Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010; 21 Suppl 5: 103-15.
42. Yamamoto N, Nakagawa K, Nishimura Y, *et al*. Phase III study comparing second- and third-generation regimens with concurrent thoracic radiotherapy in patients with unresectable Stage III Non–Small-Cell Lung Cancer: West Japan Thoracic Oncology Group WJTOG0105. J Clin Oncol 2010; 28: 3739-45.
43. Segawa Y, Kiura K, Takigawa N, *et al*. Phase III trial comparing docetaxel and cisplatin combination chemotherapy with mitomycin, vindesine, and cisplatin combination chemotherapy with concurrent thoracic radiotherapy in locally advanced non–small-cell lung cancer: OLCSG 0007. J Clin Oncol 2010; 28: 3299-306.
44. Vokes EE, Herndon JE 2nd, Kelley MJ. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: Cancer and Leukemia Group B. J Clin Oncol 2007; 25 (13): 1698-704.
45. Kim S, Kim M, Choi E, *et al*. Induction chemotherapy followed by concurrent chemoradiotherapy (CCRT) versus CCRT alone for unresectable stage III non-small cell lung cancer (NSCLC): Randomized phase III trial. J Clin Oncol, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement): 7528, 2007.

46. Hanna N, Neubauer M, Yiannoutsos C, *et al*. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. J Clin Oncol 2008; 26 (35): 5755-60.
47. Perez CA, Stanley K, Rubin P, *et al*. A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat-cell carcinoma of the lung. Preliminary report by the Radiation Therapy Oncology Group. Cancer 1980; 45: 2744-53.
48. Curran W, Scott C, Langer C, *et al*. Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemo-radiation for patients with unresectable NSCLC: RTOG 9410. ASCO 2003; 22: 621a.
49. Onishi H, Shirato H, Nagata Y, *et al*. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small-cell lung cancer: Updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007; 2: S94–S100.
50. Bradley J, Graham MV, Winter K, *et al*. Toxicity and outcome results of RTOG 9311: A phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma. Int J Radiat Oncol Biol Phys 2005; 61: 318-28.
51. Bradley J, Moughan J, Graham MV. A phase I/II radiation dose escalation study with concurrent chemotherapy for patients with inoperabile stage I to III NSCLC: a phase I results of RTOG 0117. Int. J. Radiation Oncology Biol Phys 2010; 77 (2): 367-72.
52. Schild S, McGinnis W, Graham D, *et al*. Results of a Phase I trial of concurrent chemotherapy and escalating doses of radiation for unresectable non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2005; 63: S44.
53. Socinski MA, Blackstock AW, Bogart JA, *et al*. Randomized phase II trial of induction chemotherapy followed by concurrent chemotherapy and dose-escalated thoracic conformal radiotherapy (74 Gy) in stage III non-small-cell lung cancer: CALGB 30105. J Clin Oncol 2008; 26: 2457-63.
54. Bradley J D., Bae K., Graham MV, *et al*. Chemotherapy for patients with inoperable non–small-cell lung cancer: RTOG 0117. J Clin Oncol 2010; 28: 2475-80.
55. van Baardwijk A, Wanders S, Boersma L, *et al*. Mature Results of an Individualized Radiation Dose Prescription Study Based on Normal Tissue Constraints in Stages I to III Non–Small-Cell Lung Cancer. J Clin Oncol 2010; 28: 1380-6.
56. Ramella S, Maranzano E, Frata P, et al. Radiotherapy in Italy for Non-Small Cell Lung Cancer: patterns of care survey. Tumori 2012; 98 (1): 66-78.

Received: 29.11.2012
Accepted: 5.2.2013
Address: Sara Ramella
Radioterapia Oncologica,
Università Campus Bio-Medico di Roma, Italy
Tel. 0622541420
Fax 0622541433
E-mail: s.ramella@unicampus.it