

Is an evidence-based approach realistic in non-small cell lung cancer (NSCLC)?

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Key words NSCLC, sequential and concomitant chemo-radiotherapy, pN2 disease, targeted agents

Summary

Non-small cell lung cancer (NSCLC) is a heterogeneous tumour. A wide variety of treatment options is currently available. Surgery remains the mainstay of curative treatment and an operative approach will be selected in function of disease stage, tumour resectability and performance status of the patient. Adjuvant chemotherapy is considered standard at least for stage II and III disease. In stage III disease, resectability should be decided in function of the cytological/histological confirmation of N2 disease. If N2-disease cannot be highlighted at work-up, the patients are submit-

ted to surgery followed by adjuvant chemotherapy. If patients are staged pN0-pN1 after surgery, postoperative radiotherapy should not be given. However, if pN2 is discovered at surgery, there might be a place for postoperative radiotherapy but this still needs confirmation. In case of cytological/histological confirmation of pN2 disease prior to surgery, patients should not be operated but treated with a combination of concomitant chemo-radiotherapy. This treatment algorithm will be evaluated by reviewing the published evidence issued from randomized controlled trials.

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Introduction

NSCLC is one of the most frequently occurring tumours worldwide and unfortunately has a dismal outcome. In the last decades a lot of efforts have been dedicated to optimal staging and it is controversial whether the recent improvement in outcome is related to therapeutic efficacy or stage migration. NSCLC represents a very heterogeneous group of tumours. Considerable efforts have been put in the formulation of more clear-cut definitions of sub-stages in order to optimize the therapeutic approach.

One of the key points in staging is the evaluation of nodal invasion. The therapeutic strategy and especially the decision to submit the patient to surgery depends on the presence of lymph node invasion. The gold standard in staging remains the cytological/histological confirmation of (mediastinal) lymph node invasion.¹ Various techniques with different sensitivity, specificity, positive and nega-

tive predictive value can be used. The discussion on which technique preferentially used for nodal staging is beyond the scope of the present article. We will merely concentrate on the therapeutic approach provided there has been an adequate assessment of the lymph node stage.

The treatment for NSCLC consists of surgery, radiotherapy and chemotherapy. More recently, the therapeutic arsenal has widened with the introduction of targeted agents. The choice of treatment depends on the initial tumour stage, the resectability, the age and the performance status of the patient.

The patients are eligible for primary surgery if there is no evidence for lymph node involvement at diagnostic work-up. After surgery and according to the pathological staging, adjuvant treatment should be discussed.

Patients confirmed to have pathological nodal invasion should probably not be submitted to upfront

surgery. In this patient population an induction treatment should be proposed which could eventually lead to a surgical option. although one can doubt about the impact of surgery if the metastatic potential of this tumour is already expressed.

Patients who are not a good candidate for a surgical approach, whatever the possible reason, should be submitted to a treatment combining chemotherapy, radiotherapy and possibly agents targeting specific molecular pathways known to be overexpressed or heavily involved in tumorigenesis, acquisition of an invasive and/or metastatic profile and resistance to treatment.

For these three particular patient populations we intend to review whether a consensus can be found in the published literature which could serve as possible evidence based standard approach for the use of radiotherapy.

The standard treatment for patients submitted to surgery

There is an overwhelming amount of data issued from randomized controlled trials (RCT) on the effect of adjuvant chemotherapy after surgery for NSCLC.²⁻⁴ Adjuvant chemotherapy seems to be effective especially in pN1 and pN2 disease.⁵ It is beyond the scope of this paper to discuss which chemotherapy schedule is the most effective in this setting.

The observation of a high incidence of relapse in the lung opens the question on the possible advantage of postoperative radiotherapy. The *Post Operative Radiotherapy meta-analysis (PORT)* indicates a possible deleterious effect of radiation therapy after surgery.⁶ However, many criticisms need to be addressed to the authors of this meta-analysis whereas it claims that radiotherapy is harmful without considering crucial variables such as radiation technique, beam energy, total dose, dose per fraction, overall treatment time and last but not least the volume of irradiated tissue.⁷ The trials used in the PORT meta-analysis are trials issued from the eighties and earlier. Seven of the nine trials included in the PORT study used Co⁶⁰ units. Therefore, data obtained from trials with obsolete radiation techniques cannot be considered directly relevant to contemporary practice. The deleterious effect demonstrated in the PORT study can be explained by a fatal process that appears between three months and one year after treatment.⁷ This is the time frame in which radiation pneumonitis appears. This treat-

ment related complication heavily depends on the irradiated volume, total dose and dose per fraction. In the *Surveillance Epidemiology End Results (SEER) database*, adjuvant PORT is beneficial in pN2 disease (HR= 0.86, 95% CI = 0.76-0.96; p= 0.008).⁸ In contrast, for N0 and N1 disease the effect of PORT is potentially detrimental with a hazard ratio (HR) significantly above 1. This detrimental effect has recently been confirmed by the Meta-Analysis Group of the *MRC Clinical Trials Unit*.⁹ The question whether adjuvant RT is beneficial in pN2 disease is currently under investigation in the *LungART IFCT 0503 trial*.

In the modern trials on adjuvant chemotherapy, one cannot evaluate the possible impact of radiotherapy. First of all, these trials are not designed to answer this question. Secondly, the radiation treatment technique is not standardized and there is no quality control. It is disturbing that even when radiation therapy has been allowed within the trial context, there has been no description at all of the technique and the radiation schedule used. It looks like the authors are considering that radiotherapy does only offer a placebo effect. Thirdly, as the radiotherapy technique was not standardized and not considered as a stratification factor in these trials, one cannot perform a reliable subgroup analysis as selection bias obviously must have been present. Considering all possible pitfalls, it is interesting and at least hypothesis generating to observe that the 5-year overall survival in the *Adjuvant Navelbine International Trialist's Association (ANITA) trials* reaches 47% compared to 34%, in favour of adjuvant PORT in pN2 patients receiving chemotherapy.¹⁰ The difference is less impressive in patients not receiving chemotherapy (21% versus 17%). Hence, the impact of radiation therapy might be more important in patients for whom chemotherapy is able to control distant metastases.

As far as adjuvant treatment is concerned, the take home message is the following: chemotherapy should be considered standard in stage II and III. It is not really evident whether older patients benefit from adjuvant therapy as toxicity can be cumbersome. Retrospective analysis of the impact of age reveals that elderly patients (> 65years) are less exposed to adjuvant chemotherapy. However, the effect on outcome in this elderly population is similar to the one observed in younger patients.¹¹ Adjuvant radiotherapy in the setting of adjuvant chemotherapy in the treatment of pN2 disease awaits investigation in a RCT. However, more emphasis should be

put on standardization and quality control as far as radiotherapy is concerned.

Induction treatment in NSCLC

If upfront surgery cannot be performed, some investigators are considering a neo-adjuvant approach. About 15% of the NSCLC patients are diagnosed with stage IIIA-N2 disease. In theory, patients with this stage of disease are not considered good candidates for surgery. On the other hand about 25% of stage cT1-T3/N1 will have occult N2 disease highlighted at the detailed analysis of pathological specimens after surgery. These numbers are obviously arguing in favour of neo-adjuvant chemotherapy. The meta-analysis of RCT on neo-adjuvant chemotherapy shows a HR of 0.88 (95% CI= 0.76-1.01, p not significant and no significant heterogeneity between trials).¹² The relative improvement in survival at 5 years is 2% at most which translates in a possible absolute improvement of 5%. Considering trials dedicated to patients with stage IIIA, the benefit vanishes over time. Therefore, the issue is still to be considered unanswered.

The issue of the optimal approach for stage IIIA has been investigated in various RCTs. In the *RTOG 89-01 trial* patients with stage IIIA (with cytological/histological confirmed N2) are submitted to induction chemotherapy (CDDP + Vinblastine), followed by a randomization between surgery and radiotherapy, followed by consolidation chemotherapy.¹³ Only 75 patients were randomized and there was no difference in outcome between both local modalities.

The same question has been raised by the *Intergroup trial 0139*.¹⁴ Patients with stage IIIA/pN2 are exposed to induction chemotherapy (CDDP + Etoposide) combined with radiotherapy (45 Gy / standard fractionation) followed by randomization between surgery or complementary radiotherapy. After local treatment, all patients receive consolidation chemotherapy. The five-year survival rates are not significantly different between both arms: 27.2% for surgery versus 20.3% for radiotherapy (HR= 0.63, 95% CI 0.36-1.10, p-value 0.10). An interesting observation in the intergroup trial is the impressive 3-year survival observed in patients down staged from pN2 to pN0 disease (50%). The loco-regional recurrence rate is lower in the radiotherapy arm (13%) as compared to patients submitted to surgery (21%).

The *EORTC 08941 trial* also raises the question whether surgery should be preferred in stage IIIA-

N2 after three cycles of neo-adjuvant chemotherapy.¹⁵ Again, there was no significant difference in overall survival and in progression free survival between surgery and radiotherapy (respectively 15.7 versus 14%, HR=1.07, 95% CI = 0.84-1.35). The EORTC trial raises different intriguing questions.¹⁶ What is the role of limited surgery, especially after downstaging? What is the optimal radiation therapy schedule i.e. fractionation, total dose and timing? What is the optimal treatment volume to be irradiated? What is the optimal neo-adjuvant chemotherapy? What is the optimal chemotherapy to be combined with ionizing irradiation? What is the exact role of consolidation chemotherapy?

In conclusion, the take-home messages from RCT are the following: neo-adjuvant chemotherapy alone provides a modest “all stages” survival benefit which does not exceed 5% at 5 years and is comparable to the benefit with adjuvant chemotherapy, although populations of patients are hardly comparable. Patients with stage IIIA-N2 disease are best treated with a combination of chemotherapy and radiotherapy, in view of the lower toxicity and mortality of this approach. How these modalities are optimally integrated will be discussed in the next paragraph.

Non-surgical treatment in NSCLC

Patients not eligible for surgery can be offered combined chemotherapy and radiotherapy with curative intent. We are currently facing three generations of clinical trials.¹⁷ The first generation is establishing the role of induction chemotherapy sequentially followed by radiation therapy. Among all these trials, three trials show a significant increase in 2-year survival. In a RCT, *Dillman* observed a significant increase in survival from 13 to 26% when a comparison is made between radiotherapy and sequential chemotherapy and radiotherapy (p= 0.012).¹⁸ In a larger trial comparing RT alone versus sequential CT and RT followed by CT, *Le Chevalier et al* report a similar survival increment (14 versus 21%, p< 0.05).¹⁹ In a third trial published by *Sause et al*, the 2-year survival reaches 29%, which is significantly superior to the radiation therapy alone arms (conventional fractionation or hyperfractionation).²⁰ In contrast, all other trials testing the concept of sequential chemotherapy followed by radiotherapy do not report a significant survival difference.¹⁷

The second generation of trials aims at investigating the effect of concomitant chemo-radiation compared with radiotherapy alone. Four trials are

reporting a positive impact on survival while in the other trials such a difference has not been observed.¹⁷ In the trial reported by *Cakir et al*, radiotherapy is compared to radiotherapy plus CDDP applied in week 1 and 6. The difference in survival is in favour of the combined approach (22% versus 8%, $p=0.0006$).²¹ In the trial published by *Schaake-Koning*, the best median 2-year survival (29%) is observed after radiotherapy combined with daily CDDP. The two other arms in the trial yield lower survival rates (13% after RT alone and 19% after RT and weekly CDDP).²² The positive result might be related to the frequent administration of CDDP (daily 6 mg). Another trial confirms the beneficial effect of repeated low-dose daily carboplatin combined to radiotherapy. The two-year survival reaches 43% as compared to 26% ($p=0.021$).²³ The same author reports on another positive trial comparing hyperfractionation (HFX) to HFX and low dose weekly carboplatin and etoposide versus HFX and high bi-weekly chemotherapy.²⁴ The high bi-weekly chemotherapy arm yields a survival of 37%, significantly higher than the other arms of the trial.

The third generation of trials compares the sequential and concomitant approach. The first trial showing an advantage in favour of the concomitant approach is the one reported by *Furuse et al*.²⁵ In the sequential arm vindesine, cisplatin and mitomycin is followed by conventional radiotherapy (28 x 2 Gy). In the concomitant arm the radiotherapy is non “conventional” as there is a planned treatment interruption of 10 days between two “cycles” of radiotherapy, each delivering 14 x 2 Gy. Interruption of radiation treatment has a potentially deleterious effect as repopulation of surviving clonogens during the “gap” period will reduce the anti-tumour efficacy. The median survival increases from 13.3 to 16.5 months ($p < 0.04$). The *RTOG 94-10 trial* (reported but not yet published) is a three-arm randomized trial comparing a sequential approach versus two concomitant schedules, one with conventional once daily irradiation and one with twice daily irradiation.²⁶ The best median survival is observed in the arm combining chemotherapy and once daily radiotherapy. The 4-year survival reaches 21% compared to 12% in the sequential arm ($p=0.046$). In contrast, the difference is not significant between the sequential arm and the concomitant arm with twice daily irradiation (12% versus 17%, $p=0.296$). A smaller trial published by *Zatloukal et al* tested the beneficial effect of vinorelbine and cisplatin added concomitantly to radiotherapy.²⁷ The trial is posi-

tive with a significant difference in median survival (16.6 months versus 12.9 months, $p=0.02$). However, the most recent trial published by *Fournel et al* is negative. In this trial concomitant radiotherapy (CDDP plus etoposide) does not yield a significant survival advantage as compared to the sequential approach (CDDP plus vinorelbine) (16.3 months versus 14.5 months).²⁸ The *EORTC 08972 / 22973 trial* designed to investigate the difference between the sequential versus the concomitant approach has been closed prematurely. Its results will be pooled with a similar Dutch trial.

A meta-analysis has recently been published.²⁹ This meta-analysis has been performed with individual patient data (IPD). The overall HR is 0.83 in favour of the concomitant approach (95% CI 0.73-0.94, $p=0.0026$). The risk reduction of 17% translates in an absolute survival benefit at 5 years of $4.7 \pm 2.0\%$. Another meta-analysis based on IPD has been presented at the IASLC meeting in 2007 and confirms the superiority of the concurrent approach. Compared with the sequential approach, there is an increased risk of acute toxicity with the concomitant approach due to the accumulation of independent toxicities.

The take home message concerning the non-surgical approach is the following: the concomitant approach combining chemotherapy and radiotherapy should be preferred over the sequential approach. This seems to be confirmed by both meta-analyses. The absolute benefit at 5 years, although statistically significant, remains clinically modest (+5%).

Special issues in the non-surgical approach

One way to intensify the sequential approach is to apply combined chemo-radiation after induction chemotherapy compared to radiotherapy alone after induction chemotherapy. This concept has been tested in the *CTRT 99/97 trial*.³⁰ Patients were submitted to induction chemotherapy (paclitaxel plus carboplatin). Patients not progressing after induction chemotherapy were randomized between radiotherapy alone (60 Gy) or radiotherapy combined with weekly paclitaxel. The primary endpoint was survival, but the difference in survival was not significant (HR+0.76, 95% CI:0.56-1.05, $p=0.09$). Although progression free survival was not the primary endpoint of this trial, a significant difference in progression free survival (HR+0.57, 95% CI:0.42-0.79, $p < 0.001$) was observed. Moreover, one should be aware that response evaluation has only been per-

formed with CT and quality control of radiotherapy has been done after completion of the treatment.

Another way to increase treatment intensity is to precede concomitant radio-chemotherapy by induction chemotherapy. This approach has been tested in the *CALGB 39801 trial*.³¹ A standard approach of radiotherapy (66 Gy) combined with synchronous chemotherapy (paclitaxel plus carboplatin), has been compared with two cycles of induction chemotherapy followed by the same concomitant chemo-radiation as in the reference arm. The survival analysis by intent to treat does not show a trend towards a survival benefit.

Treatment can become even more aggressive by adding chemotherapy after concomitant chemo-radiation. Several randomized phase II trials have compared the induction versus the consolidation approaches, preceding or following concomitant chemo-radiotherapy. Their results are difficult to compare due to differences in trial design and drug regimens, but suggest both approaches are feasible, although associated with a higher rate of haematological and oesophageal toxicities.

Finally, the *Hoosier Oncology Group study (HOG LUN 01-24/USO-023)* compared observation after concomitant chemo-radiation (Etoposide + CDDP + 60 Gy) with the same schedule followed by 4 cycles of “adjuvant” docetaxel.³² The mature survival data of this trial however show an inferior outcome of the intensified approach because of a higher treatment related toxicity. In conclusion, treatment intensification in the context of a sequential or concomitant approach does not yield a significant survival benefit.

Targeted agents in NSCLC

Targeted agents and especially the ones directed against the epidermal growth factor receptor (EGFR) have mainly been combined with chemotherapy.³³⁻³⁷ Data with radiotherapy are scarce and premature. There is currently one ongoing randomized trial (*RTOG 0324 / CALGB 30407*) testing the possible impact of combining a targeted agent (cetuximab) and concomitant radio-chemotherapy (weekly paclitaxel). The two other arms in this trial are radiotherapy combined with perimetrexed and carboplatin, and radiotherapy, combined with perimetrexed, carboplatin and cetuximab. One can obviously argue that interpretation of trial results will be difficult as different treatment parameters have been changed from one arm to the other in this

three arm trial. In the *S0023 trial* gefitinib has been compared with placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III NSCLC. In this “unselected” population, gefitinib did reduce survival and the effect was a result of tumour progression and not gefitinib toxicity.³⁸ This unexpected observation calls for caution when introducing targeted agents in unselected patient populations.

What about improving radiation therapy?

The current standard of care for thoracic radiotherapy in stage III NSCLC has been established in the early eighties. It is frustrating that in most trials the radiation therapy schedule has fundamentally not been changed. Already, in 1991 *Arriagada et al* report a disappointing local disease eradication rate of only 17% after doses of 60 to 66 Gy.¹⁹ It is estimated that to obtain a tumour control probability of 50% with radiotherapy in NSCLC a dose of 84 Gy is required.³⁹ However, with elective nodal irradiation, this total dose cannot be applied. One should realize however that the incidence of isolated nodal recurrence does not exceed 6%, highlighting the possible effect of incidental dose to clinically negative nodes from conformal treatment fields.³⁹ This issue has recently been confirmed in a RCT.⁴⁰ More recently, emphasis has been put on the evaluation of feasibility to escalate the dose and to combine chemotherapy with high-dose radiotherapy (≥ 74 Gy).⁴¹ Dose-escalation is made possible by technical improvements especially in the field of the definition of the target tissue. Attempts have been made to optimize the duration of radiotherapy. The *CHART-trial* confirms that continuous hyperfractionated accelerated radiotherapy is superior to conventional radiotherapy in achieving local tumour control and survival in locally advanced NSCLC.⁴¹ Moreover, the effect on distant metastases illustrates the importance of obtaining local control in this disease. In contrast, *Ball et al* failed to show a significant survival advantage for any of the treatment arms or factors in the final report of the *Australian multi-centre trial* on accelerated radiotherapy with or without concurrent carboplatin in inoperable NSCLC. The reduction of the overall treatment time only yields an increase in oesophageal toxicity.⁴²

Moreover, techniques of highly conformal radiotherapy combined with close monitoring of patient positioning reduce the risk of unacceptable acute

Key messages for clinical practice

1. Adjuvant chemotherapy is recommended in stage II and III NSCLC.
2. Adjuvant postoperative radiotherapy should be avoided in pN0 and pN1 disease.
3. The role of adjuvant postoperative radiotherapy has to be investigated in stage III with pathological confirmation of pN2.
4. Chemo-radiotherapy without surgery is the standard approach in case of stage III disease with pathological confirmation of N2 at initial work-up.

and late toxicity. Taking into account respiratory motion and gating the treatment accordingly, or even tracking the tumour with linear accelerators mounted on robotic arms, allows for more narrow safety margins and hence less healthy tissue within the high-dose region. The time has come to define adequately the appropriate radiotherapy regimen to be combined with effective systemic chemotherapy and targeted agents.

Conclusions

There are several treatment options available for patients with NSCLC. Surgery nowadays remains the mainstay of treatment for patients with early stage disease without arguments in favour of lymph node involvement. In pathological stage II and III disease adjuvant chemotherapy is recommended. Adjuvant radiotherapy should be avoided in pN0 and pN1 disease as it is potentially deleterious on survival.

In more advanced stage disease and especially in stage III NSCLC, the initial therapeutic decision will depend on the cyto-histological confirmation of pN2. For patients without cyto-histological confirmation of pN2, adjuvant postoperative chemotherapy is standard. The advantage of postoperative radiotherapy has to be investigated in pN2 disease in a RCT.

If pN2 is confirmed at diagnostic work-up, patients should be submitted to concomitant chemo-radiotherapy. Surgery in this setting does not offer a survival benefit. Intensification of non-surgical treatment such as induction chemotherapy prior to chemo-radiation or adjuvant chemotherapy after combined chemo-radiation cannot be considered standard nowadays. This has to be tested in well

designed RCT.

Newer approaches such as the use of targeted agents, bioreductive compounds, dose escalation in radiotherapy merit investigation in well designed RCTs. A better selection of patients based on validated predictive markers is a prerequisite for a successful trial in these fields.

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