Induction Therapy in Non Small Cell Lung Cancer: A Comparison of Clinical and Post-Surgical Staging

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P.L. GRANONE, S. MARGARITORA, A. CESARIO, D. GALETTA

Division of Thoracic Surgery
Catholic University of Rome

Abstract

In the last decade, several neoadjuvant trials for NSCLC patients with mediastinal lymph node involvement (N2) have been scheduled. The uniform plan is based on clinical staging, therapy, clinical re-staging, surgery (when is possible) and, finally, pathological staging. The precise classification of tumor during the three different staging procedures is mandatory. Considering clinical re-staging and pathological staging, nowadays surgery could be considered correct for most of the patients enrolled in the neoadjuvant protocols including cases where a major clinical response has not been achieved. Several experiences demonstrated how often the clinical re-staging overesteems neoplastic tissue by fibrosis and scar and could judge as unserectable patients with a minimal residual disease.
Key words: Lung cancer, neoadjuvant therapy, N2 patients, staging, re-staging.

Introduction

The neoadjuvant or, more properly, "induction" therapy (IT) can be defined as a systemic cytoreductive treatment, given to the patient pre-operatively. In the last ten years, many IT studies in NSCLC with mediastinal lymph node involvement have been planned and carried out, on the basis of the encouraging preliminary results. These tumours are classified as N2 and staged IIIa or IIIb according to the dimensional and infiltrative characteristics of the tumour mass: this classification remained unchanged in the recent revision by Mountain[1]. The patients enrolled in a IT protocol should follow a very well designed and uniform plan: clinical staging, therapy, clinical re-staging with the evaluation of response, surgery and pathological staging in the resected cases. These steps are clear and accepted in all the Institutions and the comparison of the results is connected with the respect of the precise classification according to the TNM staging of each tumour inside the three different staging procedures: clinical, clinical post IT, pathological (post-surgical) staging.

Clinical staging

A correct clinical staging is very important to identify an N2 NSCLC and to consider the case to be enrolled in a IT protocol. In all the Centres, a standard chest X ray, fiberoptic bronchoscopy, CT scan of the thorax (for the study of T and N parameters) and upper abdomen, liver US and bone scan (to check for possible metastases) are commonly undertaken. There are, however, some differences in the staging procedures.

Riassunto

Nell'ultima decade, numerosi studi clinici di terapia neoadiuvante sono stati intrapresi per pazienti affetti da carcinoma del polmone non a piccole cellule (NSCLC) con coinvolgimento linfonodale mediastinico (N2). Il protocollo si articola, uniformemente, nelle seguenti tappe: stadiazione clinica, trattamento, ri-stadiazione clinica, intervento chirurgico (quando giudicato realizzabile), stadiazione postchirurgica. È pertanto indispensabile un'attenta classificazione della neoplasia in ciascuno dei tre differenti momenti di stadiazione. Il confronto tra ri-stadiazione clinica e stadiazione postchirurgica, consente attualmente di proporre alla chirurgia la maggior parte dei pazienti trattati con neoadiuvante compresi i casi che dimostrano una modesta risposta clinica al trattamento. I rilievi della letteratura, infatti, hanno dimostrato il consistente rischio di sovrastimare la malattia residua attraverso i processi di ri-stadiazione clinica, a causa della formazione di tessuto cicatriziale e processi di fibrosi. Ciò determinerebbe l'esclusione dall'atto chirurgico di pazienti con minima malattia residua e che si gioverebbero pertanto del trattamento.
Parole chiave: Carcinoma del polmone, terapia neoadiuvante, pazienti N2, staging, re-staging.

N2 lymph-nodes identification

In some expenences[2, 3] mediastinal lymph nodes are considered to be pathologic when the CT scan assessed minor axis diameter is greater than 2 centimetres, but, in the vast majority of the reported experiences[4, 8], the limit value is considered to be 1 centimetre.

N2 lymph-nodes histo or cytological confirmation

This step should be considered to be the most important to enrole a case in an IT protocol, but it is not always accomplished. In fact, mediastinoscopy is not carried out routinely and, when performed, it cannot give any assessment about the lymph node stations number 5, 6, 8 and 9. The Video-Thoracoscopy (Video Assisted Thoracic Surgery - VATS) has sometimes been used to get mediastinal lymph-node samples for histologic assessment[9-11]. Anterior thoracotomies or CT guided FNAB (Fine Needle Aspiration Biopsy) are seldom used[11]. So, there is the chance to enrole in a IT protocol patients with enlarged, but not metastatic, mediastinal lymph-nodes with an obvious bias in the long term survival results.

Brain metastases assessment

Even if very often the brain CT scan is routinely performed, some Authors[5, 8] prescribe it only when neurological symptoms are present. In the reported experience by Strauss[4], the brain CT scan remains unmentioned. In this cases, patients with unidentified or symptomless brain metastases could be erroneously enrolled in an IT protocol.

Re-staging and assessment of the "clinical" response

Two to four weeks after the completion of the IT protocol, the patients undergo a new set of exams, to assess the response to the treatment and to check for the onset of new metastases. Usually no invasive exams are performed during re-staging, unless resectability is unclear. In these cases a mediastinoscopy or a VATS procedure can be indicated[12]. Redo-mediastinoscopy to repeat lymph-node biopsy in those stations where tumour was demonstrated has been proposed[9] and sometimes performed[13], but until now, it is not routinely performed.

Induction therapy response evaluation

When clinical restaging is completed, it is possible to make a comparison between the findings before and after IT. Usually, the cases are divided into four main groups:

– *Complete Response* (cCR): no more radiological findings of residual tumour;
- *Partial Response* (cPR): value of the tumour perpendicular diameters product reduced by more than 50%;
– *No Change* (cNC): value of the tumour perpendicular diameters product reduced by less than 50% or increased by less than 25%;
– *Progression of disease* (cDP): tumour perpendicular diameters product increased by more than 25% or if there is the appearance of new neoplastic lesions.

When, in the different reported experiences, an index of Major Response (cMR) is reported, it is referred to the sum of "Complete + Partial" responses (cCR + cPR).
This classification is accepted and adopted by many authors. A "Minimal response" is described by Martini[14] when the reduction in the tumour volume is < 50%. Kirn[15] defines the "No Change" group as those patients where the tumour mass gets bigger but no more than 15% (whilst 25% is the value reported by most). Over these little differences, we can say that the described classification is homogeneously accepted.

Pathological staging

The specimen examination in the resected cases gives the data for the last staging of the IT protocols, according to the TNM guidelines. By comparing these data with clinical staging and re-staging, it is possible to assess the ultimate effect of the IT protocol on the disease. Where no tumour is found, either in the lung parenchyma, either in the hilar and mediastinal lymph-nodes, the case is p-staged T0N0, and a "Complete Response" (pCR) is obtained. Where only microscopic neoplastic foci are found in the lung, the case is p-staged T1N0 or T_{mic}.
A "Downstaging" is obtained when the pathological assessment demonstrates a lower stage than the clinical one.

The comparison of different staging

In the last ten years, the IT protocols have been mainly used in the N2 NSCLC, clinically staged IIIa or IIIb according to the T value. The efficacy of the various IT protocols adopting chemo or radio-chemotherapy is firstly evaluated at the moment of the clinical re-staging. When only the bigger reported experiences are analysed, we observe "Major Response" rates that are somewhat different. For chemotherapy-only based regimens, the range of cMR obtained is 54% (Kirn[15]) to 87% (Mathisen[9]); for radio-chemotherapy protocols it is 51% (Strauss[4])to 85% (Rush[6]). In the cases of cMR the cCR and cPR ratio is variable with differences sometimes low (Kirn[15] reported a 10% value of cCR versus 44% of cPR) and sometimes higher (Rush[6] reported a 80% value of

cPR versus 5% of cCR and Strauss [4] a 51% value of cPR versus 0% of cCR).
The results are different when the pathological staging is compared too. In fact the 4% value of pCR in the Kirn[15] and Rosell[5] experiences is not confirmed in that of Faberg [3] where a 27% value of pCR is reported.
Anyway, it is really interesting to make a comparison between the clinical re-staging and the pathological staging data. Pujol[2] alone, in fact, reports a precise correlation of cCR with pCR: in the five patients where no radiological remnants of tumour were detected at the moment of clinical re-staging, the pathological examination confirmed the absence of tumour. In the other evaluated experiences, significant differences are, on the contrary, reported.
Rush[6] reports a 5% cCR value versus a 23% pCR while Rosell reports a 7% of cCR value versus a 4% of pCR. Sometimes the values are equivalent by chance: Burkes[7], in fact, obtained 3 pCR and 3 cCR but only one cCR was confirmed to be a pCR because in the other two cases some neoplastic remnants (as microscopic foci) were found at the moment of the pathological examination. The other pCR cases, at the moment of clinical re-staging, had been classified as cPR.
Several Authors agree about the very little predictive value on the index of tumour reduction of the clinical re-staging. In fact, the precise difference in the number of cCR when compared with the number of pCR is only sometimes reported (Rush[6]) and sometimes investigated (Yashar[12]). In this experience, Yashar reports how, in 4 of the 10 cases of pCR, some radiological findings of tumour remnants had been reported. Martini[14] put the focus on the fact that on the whole number of 19 pCR, only 5 were cCR, and the remaining 14 cPR. Strauss[4], who didn't report any cCR, got 4 pCR (3 in cPR and 1 in a cNC case). Moreover, in the 3 unresectable cases discovered at the time of operation for the extent of the presumed neoplastic mass, only biopsies were undertaken. No tumour was found at the moment of the pathologic examination of the biopsies, but fibrosis and necrosis, only.
All these observations demonstrate how difficult it is to distinguish, after IT is administered, the neoplastic tissue by the necrosis and scar, not only by means of the radiological evaluation at the moment of clinical re-staging, but at the time of the operation by means of the surgeon's hands, too.

Our experience[8]

Clinical Staging

In the period between January 1990 and June 1997, 91 patients with cN2 NSCLCs have been enrolled in a Radio-Chemotherapy IT protocol in our Institution. Male/Female ratio was 82:9 with an average age of 60 yrs (range 42-75 yrs). Clinical staging was assessed by standard chest X-ray, bronchoscopy, CT scan or NMR of the thorax, brain and abdomen, liver US and bone scan. In all patients the mediastinal lymph-node involvement has been cyto or histologically confirmed: by mediastinoscopy in 61 patients (67%), by left anterior mediastinotomy in 27 patients (19%) and by CT guided FNAB in 13 (14%).

Treatment

Carboplatin (CBDCA) has been used as dose intensifier and has been administered i.v. in continuous 24 hrs infusion from day 1 to day 4. The dose has been fixed at 90 mg/m2/day. The target volume has been considered to be the tumour mass, the hilar and the mediastinal lymph-node stations. A fractionated radiotherapy daily dose of 180cGy has been given five days per week with a total dose of 5040 cGy. Two to four weeks after the completion of the IT protocol the patients underwent a complete re-staging procedure and those judged to be resectable have been operated on in between the fourth and the fifth week after the end of the pre-operative treatment. Mediastinal radical lymphadenectomy has been routinely performed at the time of pulmonary resection.

Data Analysis

The response to the IT treatment, at the time of clinical re-staging has been considered to be "Complete" (cCR) when no radiological findings of the disease were assessed. The response has been considered to be "Partial" (cPR) when the product of the two major axes of the tumour mass reduced by 50% or more. A "No Change" (cNC) response identified those patients with a "Minimal Response" (tumour reduction < 50%) or with no radiological evidence of any response to the treatment. A "Progression of Disease" (cDP) has been assessed when the tumour enlargement was bigger than 25% or when distant metastases were identified.
At the time of pathological staging the response to the treatment has been considered "Complete" (pCR) when no tumour was found in any of the resected specimen. When only microscopic neoplastic foci were identified in a fibrous and scarry tissue we considered it as a "Minimal" residual disease and p-staged the case as T1. The "Downstaging" has been obtained in all those cases where pathological staging demonstrated a lower stage if compared with the clinical one.

Results

In the period between January 1990 and June 1997, 91 N2 NSCLC patients have been enrolled in the described IT protocol. 51 patients were c-stage IIIa and 40 IIIb. In

the group of the IIIa patients the T and N classification was as follows: T1N2: 45; T2N2: 19; T3N2: 28. All the IIIb patients were T4N2.
Clinical re-staging has been carried out on 88 patients, 49 IIIa and 39 IIIb. We obtained a cCR in 2 patients (2.3%), a cPR in 44 patients (50%), a cNC in 39 (44.3%) and a cDP in 3 (3.4%). The Major Response (cMR) average (Complete + Partial) was 52.3% (46/88). 49 patients have been judged to be resectable: 36 IIIa and 13 IIIb. 2 patients, both in the IIIb group, refused surgery. 47 patients underwent the operation and 45 have been completely resected. The Resectability Index (RI) referred to the whole population was 51.1% (45/88); the RI referred to the patients clinically judged to be resectable and operated upon was 95.7% (45/47).
At the time of pathological staging no tumour was found in 3 cases (6.7%) (pCR). In 20 (44.4%) patients, no tumour was found in the hilar and mediastinal lymph-nodes with residual disease in the lung mass. In this group of patients 6 cases (13.3%) demonstrated only microscopic neoplastic foci in a fibrous scar tissue. In 7 cases (15.5%) a residual disease has been detected, either in the lung mass, either in the hilar lymph-nodes (N1). We got a "Downstaging" Index (DI) of 56.4% (26/45) among the operated patients. In the IIIa group of patients the DI was 60% (21/35) and 50% (5/10) in the IIIb group.
We didn't notice, in our experience, any precise correlation between clinical re-staging and pathological staging. We had 2 cCR and 3 pCR and all of these pCR had been clinically re-staged as cPR. In the 6 cases where only microscopic neoplastic foci in the lung mass were identified 5 had been clinically restaged cPR and 1 as a cNC.

Conclusion

At the light of the reported evidences we can conclude that:
– Three different but comparable staging procedures must be scheduled when an IT protocol is planned: clinical staging, clinical re-staging after IT, pathological staging.
– The bias in the comparison of the results of the different experiences is represented mainly by the different staging procedures. For example, histologic confirmation of the N2 level involvement is not always obtained and the decision making process is made upon dimensional CT scan criteria; or, moreover, the investigation for distant metastases is sometimes not systematic (brain CT scan and bone scan are not always performed). In our opinion a not homogeneous staging procedure makes the results data, mainly the long term of survival ones, not comparable;
– Considering clinical re-staging and pathological staging, nowadays, we don't think it can be considered incorrect to indicate surgery for the most of the patients enrolled in the IT protocols including the cNC patients too. Infact several experiences, including ours, demonstrated how very often the clinical re-staging overesteems the real extent of the residual disease, with radiological diagnostics that very hardly distinguish neoplastic tissue by fibrosis and scar: in this way it is possible to judge as unresectable patients who have a residual disease that is, actually, minimal.
For these reasons we feel comfortable to conclude recommending to indicate surgery (unless clearly contra-indicated) in the most of patients who have been administered an IT protocol, not completely trusting the re-staging results, often unreal.

References

1) Mountain C.F.: *Revisions in the international system for staging lung cancer.* Chest, 1997, 111:1710-1717.

2) Pujol J.L., Rossi J.F., Le Chevalier T., Daures P., Rouanet P., Douillard J.I., Dubois J.B., Arriagada R., Mary H., Godard P., Michel F.B.: *Pilot study of neoadjuvant ifosfamide, cisplatin and etoposide in locally advanced non small cell lung cancer.* Eur J Cancer, 1990, Vol. 26 (7):798-801.

3) Faber L.P., Kittle C.F., Warren W.H., Bonomi P.D., Taylor IV S., Reddy S., Lee M.S.: *Pre-operative chemotherapy and irradiation for stage III non small cell lung cancer.* Thoracic Surg, 1988, 45:370-379.

4) Strauss G.M., Herndon J.E., Sherman D.D., Mathisen D.J., Carey R.W., Choi N.C., Rege V.B., Modeas C., Green M.R.: *Neoadjuvant chemotherapy and radiotherapy followed by surgery in stage IIIa non small cell carcinoma of the lung: report of a Cancer and Leukemia Group B phase II study.* J Clin Oncol, 1992, 10:1237.

5) Rosell R., Font A., Pifarre A., Canela M., Maurel J., Arellano A., Izquierdo J.: *The role of induction therapy (neodjuvant) chemotherapy in stage IIIa NSCLC.* Chest, 1996, 109(5 suppl.): 102S-106S.

6) Rush V.W.: *Resection of stage III non small cell lung cancer following induction therapy.* World J Surg, 1995, 19:817-822.

7) Burkes R.L., Ginsberg R.J., Sheperd F.A., Blackstein M.E., Goldberg M.E., Waters P., Patterson A., Todd T., Pearson F.G., Cooper J., Jones D., Lockwood G.: *Induction chemotherapy with mitomicin, vindesine and cisplatin for stage III unresectable non small cell lung cancer: results of the Toronto phase II trial.* J Clin Oncol, 1992, 10:580-586.

8) Granone P., Margaritora S., Cesario A., Galetta D., Bonatti P.L., Picciocchi A.: *Concurrent radiochemotherapy for N2 NSLC. Interim analysis.* Eur J Cardioth Surg, 1997, 12:366-371.

9) Mathisen D.J., Wain J.C., Wright C., Choi N., Carey R., Hilgenberg A., Grrossbard M., Lynch T., Grillo H.: *Assessment of preoperative accelerated radiotherapy and chemotherapy in stage IIIa (N2) non small cell lung cancer.* J Thorac Cardiovasc Surg, 1996, 111(1):123-131.

10) Rami Porta R., Navarro M.M.: *Surgical techniques for lung cancer staging.* Proceedings from the II International Congress of Thorax Surgery. June, 24-26, 1998, Bologna, Italy.

11) Putnam Jr, J.B.: *The role of thoracoscopy in the diagnosis and staging*

cancer. Lung Cancer, 1997, Vol. 18 Suppl. 2:21-22.

12) Yashar J., Weitberg A.B., Glicksmann A.S., Posner M.R., Feng W., Wanebo H.J.: *Preoperative chemotherapy and radiation therapy for stage IIIa carcinoma of the lung.* Ann Thor Surg, 1992, 53:445-450.

13) Mateu Navarro M., Rami Porta R., Cuesta Palomero M.: *Mediastinoscopy and re-mediastinoscopy in the pre-operative assessment of bronchogenic carcinoma.* Am J Respir Crit Care Med, 1996, 153:A679.

14) Martini N., Kris M.G., Flehinger B.J., Gralla R.J., Bains M.S., Burt M.E., Heelan R., McCormack P., Pisters K.M.W., Rigas J., Rusch V.W., Ginsberg R.J.: *Preoperative chemotherapy for stage IIIa (N2) lung cancer: the Sloan Kettering experience with 136 patients.* Ann Thor Surg, 1993, 55:1365-74.

15) Kirn D.H., Lynch T.J., Mentzer S.J., Lee T.H., Strauss G.M., Elias A.D., Skarin A.T., Sugarbaker D.J.: *Multimodality therapy of patients with stage IIIa N2 non small cell lung cancer. Impact of pre-operative chemotherapy on resectability and downstaging.* J Thor Cardiovas Surg, 1993, 106:696-702.