*Editorial*

# Restaging after Induction Therapy for Non-small Cell Lung Cancer

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## C-factor Recommended by UICC

One of the advantages of the TNM classification of malignant tumours[1] is that it does not require a minimum number of explorations. This allows the different specialists who are involved in the management of lung cancer patients to assess the anatomical extension of the disease regardless of the medical setting in which they work. A drawback of this universal applicability of the TNM classification is that it renders series of patients whose tumours are assessed with various degrees of intensity, depending on the availability or the utilization of the different staging explorations. In order to know the degree of intensity of the staging process and the validity of the classification, the Union Internationale Contre le Cancer (UICC) recommends to use the so called certainty factor (C factor)[2] (Table 1). The highest certainty in the clinical classification of untreated tumours, in the classification of recurrent tumours, and in the classification of tumours treated with induction therapy is obtained by the surgical explorations grouped in certainty factor 3 (C3). These explorations, namely, mediastinoscopy, parasternal mediastinotomy, pericardioscopy and thoracoscopy, among others, allow the surgeon to obtain tissue diagnosis of both the extension of the primary tumour and of its lymphatic spread.[3]

## Present Status Using C-factor

Recommendations regarding clinical staging based on the rational use and accuracy of the available means are periodically revised by experts and help those involved in the staging process to devise protocols in which investigations of increasing complexity are sequentially used depending on the results of simpler tests.[4,5] Despite these recommendations, the utilization of surgical procedures varies enormously among thoracic surgeons. This is especially true in the indication of mediastinoscopy or its variants to assess the involvement of mediastinal nodes. Routine mediastinoscopy is cost-effective and maximizes quality-adjusted life expectancy.[6] However, the most common policy is to perform mediastinoscopy when the computed tomography (CT) scan shows mediastinal nodes of over 1 cm in diameter.[7] The high rate of positive nodes (20%) found at mediastinoscopy in patients with no enlarged nodes on CT scan prompts a minority of groups to indicate it routinely.[8]

## Value of Induction Therapy from Past Decade

Surgical resection alone for those patients with non-small cell lung cancer (NSCLC) and mediastinal involvement faces a high rate of therapeutic failure, mainly at distant sites, and is associated with a 5-year survival rate ranging from around 20% for N2 tumours to less than 5% for N3 tumours. Selected patients with completely resected T4 tumours with no mediastinal nodal involvement have a more favourable outcome. In the past decade, several phase II studies and a few phase III trials have assessed the value of induction therapy in these groups of patients with the objective to improve survival. The former have shown that tumour downstaging and complete resection were associated with better survival.[9-12] Specifically, persistent nodal disease has a deleterious effect on prognosis, with a 5-year survival rate similar to that obtained by chemoradiation alone: 9% for patients with persistent N1-N2 disease and 35.8% for those whose tumours were downstaged to N0.[12] Results of the four published phase III clinical trials comparing induction chemotherapy followed by surgery versus surgery alone with or without postoperative mediastinal irradiation are contradictory. The earliest one, published as an interim analysis, did not find differences between both arms.[13] The two next trials had to be closed prematurely and included a limited number of patients, but both found significant benefit in terms of prolonged survival in patients treated with induction chemotherapy.[14,15] Finally, the largest trial to

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**Table 1. Certainty (C) factor**

| Factor | Description of staging methods | Applicability |
|---|---|---|
| C1 | Evidence from standard diagnostic means (e.g., inspection, palpation, and standard radiography, intraluminal endoscopy for tumours of certain organs) | cTNM, rTNM, and yTNM |
| C2 | Evidence obtained by special diagnostic means (e.g., radiographic imaging in special projections, tomography, computed tomography, ultrasonography, lymphography, angiography, scintigraphy, magnetic resonance imaging, positron emission tomography, endoscopy, biopsy, and cytology) | |
| C3 | Evidence from surgical exploration, including biopsy and cytology. | |
| C4 | Evidence of the extent of the disease after definitive surgery and pathologic examination of the resected specimen | pTNM |
| C5 | Evidence from autopsy | aTNM |

cTNM: clinical TNM classification; rTNM: pretreatment classification of recurrent tumours; yTNM: classification after induction therapy prior to definitive treatment; pTNM: pathological classification; aTNM: autopsy classification

date did not find significant differences in the group of patients with clinical N2 disease.[16)]

## Necessity of y-TNM Classification: Especially for Stage IIIA and IIIB NSCLC

Tumour response is based on the reduction of tumour volume assessed by imaging techniques, mainly CT scan. By calculating the reduction of tumour volume in relation with the volume before induction treatment, the different types of responses are defined: complete response, partial response, stable disease, or progression. There are no guidelines or recommendations for restaging stage IIIA and IIIB NSCLC after induction therapy. However, it is well-known from the clinical classification that the results of imaging techniques correlate poorly with the pathological status of the primary tumour or the lymph nodes. Despite this fact, restaging after induction therapy for stage IIIA and IIIB NSCLC is performed by CT scan, only, in most clinical trials. The initial experience with positron emission tomography (PET) to assess residual disease after induction treatment lacks accuracy to detect involvement of mediastinal lymph nodes, a key prognostic factor in this type of patient.[17)] In the last few years, some groups have initiated a more invasive restaging with remediastinoscopy in order to identify those patients in whom there remains no mediastinal disease after induction and, therefore,who would benefit most from pulmonary resection.[18-20)] Remediastinoscopy in this setting has proved to be feasible with very low morbidity and high diagnostic value: sensitivity of between 0.7 and 0.87, specificity of 1, and accuracy of between 0.8 and 0.93 have been reported.[18,19)] The results of one of these studies compared very favourably with those obtained with a CT scan for restaging: sensitivity 0.41, specificity 0.75, and accuracy 0.58.[19)] Transbronchial needle aspiration, endobronchial ultrasonography and videothoracoscopy could be alternative restaging procedures of intermediate invasiveness, but there is no experience to prove their accuracy in this clinical setting.

## Conclusion

Given the scarce evidence of the benefit of induction therapy for locally advanced NSCLC and the fact that the benefit of lung resection after induction remains to be proved, it seems thoughtful to select for lung resection only those patients for whom we know surgical treatment will improve their prognosis. So far, these patients are those whose tumours have undergone downstaging in their nodal involvement. The key issue is how to identify these patients. The few reports on remediastinoscopy show that this procedure is more accurate than any imaging technique and, therefore, it should be performed in all patients whose disease has not progressed during induction therapy.

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