The Invasive Staging and the Role of Complete Resection in the Surgical Treatment of NSCLC

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Abstract

Years of debates couldn't solve the discussion between the NSCLC assessment founded on CT scan and mediastinoscopy as in the Western countries and the refined extensive bronchoscopy, CT imaging and exploratory thoracotomy as practiced in Japan.
Recently, the clinical onset of combined therapy protocols, the recognised value of the intrathoracic staging (also in the West) and survival rates in the earlier N2 disease moved towards change this steady situation. The role of complete resection in N2 NSCLC is therefore debated from the preoperative assessment to survival results in resected cases. Accuracy of CT scan and cervical mediastinoscopy is discussed also in the light of neoadjuvant therapy. The clinical value of intrathoracic staging is improved by Japanese experiences while a rationale assessment of Complete/Incomplete Resections is defined. Moreover, technical details of intraoperative recognition are cleared.
Key words: Lung cancer, intrathoracic staging, mediastinoscopy, survival.

Riassunto

Anni di dibattiti scientifici non hanno consentito di dirimere la diatriba tra la strategia di stadiazione per il cancro del polmone adottata negli USA ed in Europa e basata sull'impiego della TC combinata all'esecuzione della mediastinoscopia, e l'atteggiamento della scuola chirurgica giapponese fondato sull'esame broncoscopico estensivo ed approfondito, la TC e, quale tappa finale, la toracotomia esplorativa con linfoadenectomia mediastinica estesa. Nel recente passato, l'adozione nella pratica clinica di protocolli combinati di terapia multimodale ed il contemporaneo riconoscimento della validità dei processi di stadiazione intratoracica finalmente anche nei paesi di cultura occidentale, accanto alla registrazione in letteratura di lusinghieri tassi di sopravvivenza nei pazienti sottoposti ad exeresi con "iniziale" coinvolgimento linfonodale mediastinico (N2 +) hanno determinato un cambiamento di questa rigida separazione di mentalità. Il ruolo della resezione a carattere di radicalità nei pazienti affetti da NSCLC e risultati N2 + viene pertanto discusso nei suoi differenti aspetti, dai processi diagnostici preoperatorii ai risultati sul piano della sopravvivenza nei casi operati. Viene altresì esaminata la accuratezza della TC e della mediastinoscopia cervicale alla luce dell'adozione dei recenti protocolli di terapia adiuvante. Il valore clinico delle procedimenti di stadia -

In 1988, with the opportunity of the First Agrigento International Conference on Lung Cancer, I was allowed to say that the risk connected with the exploratory thoracotomy becomes a lesser consideration in STAGE III tumors with an apparently resectable T component. In these cases, the evidence for selecting mediastinoscopy/tomy is limited only to the suspicion of a small cell tumor or a contralateral mediastinal spread. *Thoracotomy, instead, becomes an almost obligatory step with a specific surgical plan*: 1) to perform a complete resection of tumor with extensive removal of ipsilateral mediastinal lymph node stations and 2) to achieve an intra and postoperative Staging of disease in order to give a morphological basis for recommending adjuvant therapy[1].
These conclusions were expressing my own surgical mind which had matured deeply influenced by both the Western attitude at the M.D. Anderson Cancer Center, Houston, Texas, and the Japanese one at the National Cancer Center, Tokyo. Indeed, the former Institution was following the common Western tendency more inclined to the less aggressive Staging methodologies, namely CT imaging and cervical mediastinoscopy, with the aim to exclude from surgery all positive cases for N2 mediastinal disease. Moreover, even the intraoperative mediastinal exploration was basically conceived as a lymph node sampling mainly for staging purposes. In the Japanese Institution, the exclusion from surgery was strictly limited to a very few number of bulky N2 tumors at the CT scan. The prevalent tendency instead, was towards the exploratory thoracotomy on principle, followed by the systematic mediastinal dissection not only for staging but also for cure, even for the lower staged tumors.
Such a diverging situation was really worldwide! It was

zione intra-toracica è ribadito sulla base dell'esperienza dei gruppi di lavoro giapponesi, mentre viene d'altra parte definito il concetto di resezione completa ed incompleta. Sono presentati, infine, i diversi dettagli tecnici volti a chiarire la standardizzazione delle procedure di linfoadenectomia.
Parole chiave: Carcinoma del polmone, staging intratoracico, mediatinoscopia, sopravvivenza.

followed by years of discussion and debates mainly addressed to the difficult problem to preoperatively assess, with a due accuracy, the N2 spread of tumor, either for discovering the real extension of the mediastinal diffusion in locally advanced tumors, or, even, for excluding hidden positivities in otherwise lower staged cases. In this clinical matter, the diagnostic power was basically founded upon CT imaging and cervical mediastinoscopy for the West, while, for the Japanese, it was based upon the extensive bronchoscopy, CT imaging and the exploratory thoracotomy "on principle", followed by the systematic mediastinal dissection.

On the other hand, if one wants to consider in more detail the accuracy of the diagnostic imaging and the cervical mediastinoscopy in the light of the lower ranges (from 0 to 20%) of the historical 5yr survival in operated patients with N2, it is easy to understand the difficulty for the Western surgeons to get definitively together with more homogeneous diagnostic and therapeutic plan.

Indeed, CT scan is inaccurate 20%-30% of the time in both directions – false negative and false positive – small nodes are not always free of tumor and large nodes are often the result of inflammation rather than cancer, while around the 15% of patients staged by a cervical mediastinoscopy, still have an unsuspected N2 at the thoracotomy. Again, in line with this basic inhomogeneity, even the medical terminology commonly used in the West to present N2 Disease is as more than ever varied, such as: "bulky, limited, minimal, intranodal, extranodal, single nodal station, more nodal stations, symptomatic, clinically unrecognized, unexpected, unsuspected, unforeseen, latent, inapparent, initially recognized at thoracotomy etc.".

To critically react when commenting such a still unsettled clinical problem, Shields, in 1990[2], wrote "the significance of the presence of N2 disease in patients with non-small cell cancer of the lung is widely misunderstood". In addition, he strongly pointed out that "... it remains the goal of the surgeon to identify the small but important group of patients with N2 disease that may benefit by surgical resection and to extract these patients from the entire number of patients with N2 disease, because the majority of these patients are not primary surgical candidates".

On the other hand, considering the whole subject of N2 disease, Mountain, in 1994[3], affirmed that "the criteria for resectability may vary with the surgeon's individual philosophy or expertise or the policy of a particular institution" and " ... some physician equate clinical evidence of mediastinal adenopathy, Stage III-N2 disease, with unresectability, while others, consider complete resection an option for selected patients with this extent of disease".

In the last years this rather steady situation, has moved towards change under the pressure of three newly developed important clinical issues. They are: 1) the modern combined induction therapy protocols; 2) the progressive recognition by the Western surgeons of the clinical value of the Intrathoracic Staging and 3) the challenge of the earlier detected N2 disease.

As to the first issue, it is well known that the gradual progression of the former experiences with the induction chemo (radio) surgical treatment for Stage III-N2 NSCLC, was dramatically boosted to a world-wide expansion by 1994, when Roth[4] and Rosell[5] published the impressive results of their randomized studies, with real deserving median survivals obtained.

According to this, the search for a sound methodology for assessing the mediastinal lymphatic spread before and after the induction treatments, has confirmed the cervical mediastinoscopy and the re-mediastinoscopy as the formal tools for a proper management of these study protocols. Although the CT imaging still maintains its important diagnostic role in these cases, the pathological confirmation through the re-mediastinoscopy at the end of induction treatment, represents the only one rationale approach for evaluating the grade of Response at the mediastinal level.

The second issue of Intrathoracic Staging is expressing the progressive tendency by the Western surgical groups to get closer to the Japanese ones, recognizing an increasing role to the surgical exploration of the mediastinum at the thoracotomy, while trying to improve the curative approach through the systematic lymph nodal dissection. This issue, exhaustively discussed during the workshop on Intrathoracic Staging held in London on 1996[6], in spite of some still contrasting positions[7], will probably help to overcome the ambiguous chapter of the "unsuspected N2" cases, because discovered only at thoracotomy[8, 9, 10].

The last subject regards the new issue of the so called "early N2 Disease" which fully belongs to the Japanese research since the initial definition of the early (small-sized) peripheral or central lung cancer by Ikeda, on 1989[11]. In such a category of tumors with a diameter constantly less than 3 cm and usually discovered by means of mass screening programs, the extended mediastinal approach according to the Japanese attitude, has obtained extremely interesting results in term of both improved knowledge of the disease and the survival rate after surgery. In a series of 337 small peripheral tumors of 3 cm or less in diameter, Asamura and Naruke reported, in 1996[12], a rate of 8% N1 and 11.5% N2 in tumors of < 2.0 cm, while there was a rate of 11% N1 and 21.5%

N2 in tumors ranging from 2 to 3 cm with a whole lymph nodes involvement of 32.5%. The 5yr survival of these early detected and completely resected N2 cases in such category of small tumors, was of 44.5%! Watanabe (1996)[13], found a 15% rate of N2 in tumors of 11-20 mm, and a 24% rate in tumor of 21-30 mm. The 5yr-survival rate in operated patients with this true latent N2 was of 33%. In a comparable series of small cancers (3 cm or less in diameter) including one Tis, Tateishi reported, in 1995[14], a rate of 10% N1 and 19% N2. In these N2 resected patients 5yr survival was of 30%.

5yr survival rates ranging from 30 to 45% in operated patients with an "early N2", are extremely interesting and represent a true challenge when compared with the other category of operated N2 tumors where the mediastinal involvement is evidently more progressed but still ambiguously defined as "unsuspected", because previously unrecognized at the clinical staging[8, 9, 10].

Considering now the parallel matter of the Complete Resection, it prompts us to immediately consider two basic conditions which really represent a true challenge in the surgical approach to NSCLC: the completeness of resection and the possibility that a residual tumor, gross or microscopic, could be left behind (the Incomplete Resection).

As far as the concept of Complete Resection is concerned, we have to realize that it required a long time before maturing till the present standard. Moreover, it is intriguing to know, that most of the time was spent in carefully identifying the opposite condition of the Incomplete Resection, which had to be laboriously differentiated from the other more indeterminate but widely diffused "palliative resection". In this latter category, a series of pathological and clinical events largely inhomogeneous in between, had been loosely pooled together: the gross tumor left behind mainly due to the lack of clinical or even surgical recognition of the disease; the known distant metastases in contemporaneity with lung resection; the surgical approach aimed at relieving only symptoms by partially removing tumor, etc. On the opposite side, the corresponding definition of "curative resection" was as well indeterminate as the palliative one, mainly because the evaluation of the surgical completeness was, at that time, closely committed to the personal judgement of the surgeon. On this matter we mustn't forget that before the advent of the new Rationale for Staging Lung Cancer in 1986, a large place to personal attitude was left to the surgeons, according to the diffuse belief that.... "Resectability is a state of mind!" and.... "the decision whether to resect a particular neoplasm often depends on the respective surgeon's philosophy more than on objective facts", as Dov Weissberg wrote in 1981[15]!

The initial attempt to give a rationale assessment to the Incomplete Resection belongs to the late 70s when Shields thoughtfully decided to found this new definition upon the objectiveness of some indisputable data, such as the histological proof of the residual tumor in the ipsilateral hemi-thorax, while denying any credibility to the subjective feelings of surgeons in judging the local progression of tumor. In his well known editorial entitled "The Incomplete Resection" published in 1989[16], where he was summing up a decennial experience on this subject, he concluded that the strict definition of Incomplete Resection should derive only from the histological proof, while it is not acceptable to judge a resection incomplete, because the surgeon believes, on a theoretical basis, that the patient has a poor prognosis. Following such classifying criteria, Shields reported a one-year mortality rate of 74% in a group of 221 patients who underwent an incomplete resection, while 8.5% of them survived 3 years and 4% survived four years or more. In this last small subgroup, the 5yr. survival was of 23%, while, these patients were all showing the peculiar pathological feature of a residual microscopic disease localized on the submucosal layer (not lymphatic) of the bronchial stump, distally. With the recognition of this last peculiar category of low-stage incompletely resected but still long-term survivors, the problem of Incomplete Resection became clearer, giving in the meantime, as much clarity to the opposite figure of Complete Resection. It was closely approaching, on the way to identify with, that of a complete local and regional surgical clearance of tumor, while any other different operative results fall into the category of an Incomplete Resection.

The Complete Resection, according to such a distinctive feature, becomes also one of the most important end-points recognized by the Staging rules as the basic condition for rationally estimating the survival rate after surgery.

Fully aware of this established role within the Staging mechanism, Mountain, in 1985[17], tried to offer the first guidelines for the *apparent complete resection* in the surgical setting: 1) the surgeon is morally certain he or she has encompassed all known disease; 2) the proximal margins of the resected specimens are microscopically free from tumors; 3) within each major lymphatic drainage region, the most distal node is microscopically free from tumors; 4) capsules of resected nodules are intact.

As to the crucial matter of N2 mediastinal extension, Mountain underlined once more that, in such cases, a complete resection is actually achieved only when the most distant nodes within each major lymphatic drainage region are microscopically free of tumor and no perinodal expansion exists. Accordingly, if the farthest node in the dissection is positive for tumor, the resection has to be defined incomplete.

Unfortunately, these accurate but only clinically based guidelines on how the surgeon has to deal with the complete resection, were not universally accepted and, from the beginning, they were considered really different from the Japanese side. For the latter, the complete resection of N2 disease is represented by more extensive surgical procedures by which all accessible metastatic lymph nodes are removed even if the most distal of them

is found to be involved. It clearly means that the complete removal of the last distant involved lymph node is still considered by the Japanese within the criteria of surgical completeness.
As far as this complicated matter is concerned, we cannot help considering the different attitudes existing in the surgical world and the consequent differences in survival criteria which can result.
The mediastinal lymphadenectomy is one of the most important items still in debate.
The approach to the mediastinal lymphadenectomy is historically diverging, being basically conceived as lymph node sampling for Staging by the Western Surgeons, while pursued as a systematic mediastinal dissection for cure by the Japanese. Moreover, the Japanese have considered as routine to extend the mediastinal dissection contralaterally through a median sternotomy, when tumors are located in the left upper lobe.
In consequence of this and following Watanabe's considerations about Mountain's guidelines on the apparent complete resection, due to the different approach to their N2 component[18], a consistent number of Japanese patients would be excluded from the complete resection group, if one wants to apply Mountain's guidelines. In such cases, an improved survival rate in the Japanese Complete Resection group will immediately result, as an effect of the further statistical selection done.
As a matter of fact, we can conclude recognizing the complete resection two different basic features: on one hand, it represents the positive conclusion of a surgical approach which has helped to completely remove the tumor mass together with its mediastinal extension (N2 Disease!), by means of a series of more or less advanced surgical procedures. On the other hand, it was assumed as an well-assessed end-point of Staging System as the point in time from which the survival after cure can be objectively calculated.
As to the Incomplete Resection which ranges from 2.6 to 14.7% of all resected cases[16], the lack of clinical or, even, of intraoperative recognition of the disease as well as really unsuspected technical difficulties, are the possible causes which make a complete resection of tumor impossible. In more detail one can affirm that: 1) the gross tumor left behind represents a surgical failure, while the natural history of the disease remains unmodified with the operation; 2) the microscopic residual at the margin of bronchial stump is a more favorable clinical condition, where better 5yr survival rates, ranging from 19% with the so called "R1 group" by Vogt Moykopf[19], to 23% with the "submucosal but not lymphatic invasion group" by Tom Shields[16], have been reported; 3) as far as the intra operative frozen section microscopy is concerned, the microscopic residual at the bronchial cut-edge represents a technical failure; finally, 4) from the pure surgical point of view, a residual microscopic deposit has to be considered as a true complication which the skilled surgeon is requested to positively cope with, provided that "a proper message" from the pathologist reaches the operative theatre "still in time".
Instead, receiving the ominous result of a residual tumor one or two days after the operation, when the false negative result has been corrected by conventional staining methods, the microscopic residual tumor becomes a heavy ethical problem which deeply involves the surgeon in person. This unlucky event, which is well known to almost all experienced surgeon, requires careful attention and the ability to thoroughly inform the freshly-operated patient on the need and on the risk of an, otherwise necessary, re-opening.
Furthermore, according to what affirmed by Hasse in 1994[20], "it would be extremely difficult to discuss such problem with a patient after a false negative initial result due to a deficiency of the technical standard of frozen section examination or, worse still, the omission of what we think to be obligatory, namely the frozen section examination of all the resected bronchial margins!".

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