



## Considerations about the complete resection in NSCLC surgery. Review

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### Introduction

The local control of NSCLC by surgery prompts us to directly consider two important issues which the surgeon, he or she, is basically requested to deal with: the completeness of resection and the chance of a residual tumor, gross or microscopic, which makes the resection incomplete. The latter condition regularly escapes the surgeon's notice, becoming the real matter of concern in the local surgical control of tumor. Accordingly, the complete resection strictly depends on the clearance of any microscopic remnant still lying within the surgical margin left behind.

As the technical rule, this margin becomes safer the farther it is from the tumor borders, but the surgical procedure has basically to cope with a threefold challenge: the anatomical integrity of surrounding organs and structures, the less definite boundaries of the mediastinal lymphatic network, and the need to microscopically assess the clearance of tumor upon the surgical margin left behind. Overall, this task is not easy to achieve and, as a consequence, a safe surgical margin cannot be systematically assured to the critical boundaries of resected lung cancers.

On the other hand, any undiscovered microscopic residual tumor is expected to become an independent negative factor of prognosis as is the gross residual (1).

Nowadays the rate of local recurrence in the resected lower stages I and II NSCLC still represents a major problem (2, 3) since, besides the recognized negative role of T2 or N1 status, unrecognized microscopic residuals can also be responsible.

Therefore, it seemed of some benefit to recall the principles of the surgical completeness in NSCLC by considering, first, the following basic topics: 1) the historical background of the matter and 2) the incomplete resection due to both the microscopic residual tumor at the bronchial resection margin and the critical resection margin within the ipsilateral mediastinal lymphatic area.

### Abstract

*The complete resection for NSCLC is analyzed through the study of a series of retrospective surgical reports upon the incomplete resection, due to a microscopic residual tumor at the resection margin.*

*Following Shields' statement in 1974, the incomplete resection represents, in fact, the basic study protocol for the local recurrence following the resection of primary NSCLC. First of all, the obligation for a careful intraoperative pathologic assessment upon the resection margins, clearly emerges from this study.*

*Secondly, two main aspects featuring the incomplete resection have also been pointed out.*

*The first is represented by the historical microscopic residual tumor at the bronchial resection margin, while the second, more recently recognized, is represented by the critical resection margin within the involved ipsilateral mediastinal lymphatic area.*

*The analysis of such different figures leads to different considerations when dealing with the basic matter of the local-regional completeness of resection and the oncological result in terms of cure. In fact, while the problem of the bronchial remnant appears amenable to further improvement by activating the surgical attention, the second, instead, is to be considered unmodifiable by the surgery alone.*

*It basically depends on the extended microvasculature of the large lymphatic mediastinal network which appears to be the crucial factor of risk for such a "lymphatic" resection margin.*

*In conclusion, the matter of complete resection is still open to further research provided that the design is strictly prospective.*

*As a matter of fact, so far the expectation for cure in any apparently completely resected NSCLC is ruled by other well-known factors of prognosis which do not consider the quality of the resected margin at all.*

*Key words: Staging System and TNM classification; bronchial resection margin; mediastinal lymphatic area; N2 disease; systematic hilar-mediastinal lymph node dissection; mediastinal lymph node sampling.*

## Riassunto

### CONSIDERAZIONI SULLA RESEZIONE COMPLETA DEL CARCINOMA POLMONARE. ANALISI DELLA LETTERATURA

*Il problema della resezione completa del carcinoma polmonare viene rivisitato attraverso la ricerca in letteratura dei contributi chirurgici più significativi sulla resezione incompleta. Questa seconda condizione, infatti, sebbene solo speculare rispetto alla prima, ha il vantaggio di rappresentare fin dalla fondamentale riorganizzazione della materia ad opera di T. Shields nel 1974, il modello elettivo per lo studio delle recidive locali di malattia dopo resezione del tumore primitivo. Inoltre, il concetto di resezione incompleta richiama direttamente all'obbligo della ricerca istopatologica intraoperatoria accurata dei possibili residui microscopici di tumore sui margini di resezione, anticipando il giudizio definitivo sul materiale asportato. Lo studio di una larga serie di esperienze chirurgiche retrospettive ha permesso essenzialmente di focalizzare due quadri clinico-patologici chiaramente rappresentativi della resezione incompleta: il primo, più antico, è il residuo microscopico di tumore sul margine di resezione bronchiale ed il secondo, più recente, è la linfadenectomia critica in ambito mediastinico quando vi è infiltrazione metastatica ai linfonodi (N2).*

*Nel complesso, l'analisi dei dati disponibili ha dimostrato come il problema della resezione chirurgica completa sia tuttora aperto per quanto attiene alla esigenza oncologica della completa rimozione, macro e microscopica, della massa tumorale e delle sue radici linfatiche loco-regionali. Tuttavia, mentre nel caso del margine bronchiale a rischio, possibilità di migliorare il problema attraverso un più accurato approccio chirurgico sono state chiaramente individuate, nel caso della linfadenectomia mediastinica critica invece, risulta particolarmente difficile ammettere che la condizione principale di rischio quale è l'ampia microvascolarizzazione linfatica a livello mediastinico, possa essere mai controllata con successo mediante la sola resezione chirurgica.*

*Pertanto, l'esigenza di nuove ricerche su basi rigorosamente prospettiche, risulta evidente in questo campo. Infatti, le aspettative di cura per i carcinomi non a piccole cellule completamente resecati, rispondono oggi a criteri prognostici ben noti ma che assolutamente non riguardano la sola apparente completezza oncologica della resezione, talvolta. Parole chiave: Staging System and TNM classification; bronchial resection margin; mediastinal lymphatic area; N2 disease; systematic hilar-mediastinal lymph node dissection; mediastinal lymph node sampling.*

## Abbreviations:

NSCLC = non small cell lung cancer;  
 LCSG = Lung Cancer Study Group;  
 CIS = carcinoma in situ;  
 UICC = Intl. Union Against Cancer;  
 R1 = microscopic residual tumor;  
 ROC = roentgenographically occult carcinoma.

The recognized concept of complete resection and the updated surgical experience, were then considered, while some clinical evidence and specific references, were also pointed out.

## Historical background

The concept of "complete resection" of lung cancer, has taken a long time to be recognized in its present sense. In fact, it had to closely follow the slow evolution of surgery for lung cancer, whose first clinically relevant results with cure began to appear in the fall of 1970s (4, 5, 6, 7).

At that time, the TNM classification of lung cancer was still crude, the clinical data was largely inhomogeneous, the expectations for survival after surgery merely a sound hope and the completeness of resection nearly an individual feeling. Indeed, a large place in deciding the pulmonary resection was left to the personal attitude of surgeon, according to the widely accepted belief that "*the decision whether to resect a particular neoplasm often depends on the respective surgeon's philosophy more than on objective facts*", as Weissberg wrote in 1981 (8).

Therefore, it is not by chance if, around the fall of 1960s, T.W. Shields decided to give a more concrete definition to the complete resection, as a cornerstone issue in the surgical rationale. He focused, initially, on the opposite condition of incomplete resection, basing the related sense exclusively upon the objectiveness of the histological proof of a residual microscopic tumor in the ipsilateral hemithorax. He decided also to deny any credibility to the subjective feeling of surgeons in judging the local progression of tumor. In 1974 (9), Shields presented the results of his research which collected a group of 221 incompletely resected patients with an overall one-yr mortality of 74% and 14 of them surviving 5 years or more. The majority of this last group (no. 9) were microscopic residual tumors infiltrating the submucosal layer (not lymphatic) of the proximal bronchial resection margin.

This assessed pathologic finding coupled with a prolonged survival, ultimately gave morphologic consistency and even clinical recognition to a highly selected subgroup of patients with a microscopic bronchial remnant, who could still survive. It helped also to read the clinical reports available at the time, better.

Habein et al. (10) in 1956, were the first who reported on 18 cases of recurrence at the bronchial stump. An inadequate surgical margin, the "mucosal metaplasia", or the proximity of metastatic hilar nodes were ascribed the responsibility for the local recurrence. No long-term survivors were reported.

Cotton in 1959 (11) provided the first controlled report on the histologic pattern of the bronchial spread from the primary tumor. According to this, the safe surgical margin of distal resected bronchus was identified in a length of at least 1.9 cm.

Groves and Mc Cormack in 1962 (12), reported the first two long-term survivors with a microscopic residual squamous cell carcinoma at the bronchial stump after pneumonectomy. Both tumors, discovered shortly after the operation, were treated for years by a conservative, local chemical treatment before the final RT, obtaining a palliation of 7 and 6 years, respectively, in very good physical condition.

Hughes and Tildon in 1966 (13), reported one long-term survivors (>5 years) out of 18 with invasive carcinoma at the point of bronchial division, with 4 cases where the tumor was surely confined to the submucosal lymphatic vessels.

Jeffery in 1972 (14), reported on the first 6 cases of long-term survivors (5 years or more), out of 18 patients with a positive bronchial resection margin discovered on the resected specimens. Most of the patients received a course of adjuvant RT.

Soorae and Stevenson in 1979 (15), reported on 64 cases with a microscopic residual at the bronchial margin of the resected specimens. Four pathologic patterns were recognized: direct extension of tumor along the bronchial wall, lymphatic permeation, clumps of cancer cells in parabronchial tissues and CIS. 15 patients lived for 5 years or more: 7 out of 34 cases with direct mucosal extension of tumor, 7 out of 10 CIS, and 1 out of 6 with cell clumps in parabronchial tissues. There were no long-term survivors among the 14 with lymphatic permeation, while, intriguingly, not all the CIS reached the long-term survival group. Although rare, spontaneous regression of residual tumor through many different biologic mechanisms, was thought to bring about these prolonged survivals. Adjuvant RT was not routinely used.

Law et al. (1982) (16), reported on 64 similar cases, topographically classified in three groups: A) inner bronchial wall with both CIS or direct mucosal invasion by the primary tumor; B) outer bronchial wall and peribronchial tissues, with direct extension of primary tumor or the invasion from nearby metastatic lymphnodes; C) lymphatic permeation alone of submucosal or peribronchial lymphatics. 6 out of 9 CIS, 9 out of the 26 invasive mucosal tumors and 1 out of the 8 with lymphatic invasion survived 5yrs or more, while none of the 18 peribronchial survived more than 3 years.

A local immunological reaction, cicatricial necrosis and even technical artifacts were called to explain the prolonged spontaneous survivals, while CIS was recognized non invasive by definition. Skeptically, the Aa. concluded that *the survival curve of mucosal invasive malignancy may combine both the unaffected survival of patients who really have no residual tumor and the poor survival of those who genuinely have tumor in the stump!*

However, although a complete agreement upon the topographic pattern of those residual tumors expected to have a long survival hadn't been reached, the confirmed recognition of some *incompletely resected but still long-term survivors due to a microscopic residual tumor at the bronchial*

*margin*, gave further clinical support to the initial Shields' recognition.

Considering now another important surgical target, the experience acquired along the years has clearly indicated that the ipsilateral mediastinal lymphatic area is a true challenge for the completeness of resection when it is dealing with N2 disease.

Mountain, fully aware of this important clinical issue, specifically considered the *tumoral extension to the mediastinal lymph nodes* (N2 disease) among the guidelines for the apparent complete resection, given in 1985 (17). Indeed, in line with the established position of the LCSG (18), Mountain emphasizes the rule that, within the mediastinal area, resection is complete only when the most distal (highest) resected node is found microscopically free of tumor. Consequently, if this last node is found positive for tumor, the resection has to be defined incomplete, even though the node had been "completely" resected.

In clear contrasting position, Watanabe et al. (19), strongly called up the Japanese surgical attitude based upon the systematic dissection of hilar and mediastinal lymph nodes, as the standard procedure for obtaining a complete resection in this area. The Japanese surgical rules (20), in fact, recognize that all accessible metastatic lymph nodes, even the most distal ones (highest), can be completely removed by such procedure. As a consequence, the approach to the mediastinal lymphadenectomy has been different for a long time, since basically conceived as a lymph node sampling for diagnosis and staging by the West, while pursued as a systematic hilar/mediastinal lymph node dissection not only for staging but also with curative intent by the Japanese.

The cultural debate on this matter is still active and, therefore, it'd better to still define as "critical" the resection margin in this area, until a final agreement is reached.

The contributions of Mountain and Watanabe, ideally conclude the historical background of the matter, while the profile of the incomplete resection resulted properly shaped by the following two significant clinical figures: *the microscopic residual tumor at the bronchial resection margin* and *the critical resection margin within the ipsilateral mediastinal lymphatic area*. Other possible sites of risky resection margins such as the thoracic wall, mediastinal organs, lung parenchima, great vessel ecc... although well recognised in the past (9, 21), are still considered less significant.

In the end, based upon such a large rationale, a suitable definition for the complete resection as the *histologically proven, complete surgical clearance of any resectable M0 NSCLC*, also clearly came out.

## Updated surgical experience

Heikkila et al. were the first who tried, in 1986 (22), to correlate the spontaneous survival of bronchial residual tumors with the expected survival according to the stage

of disease. There were 44 long term survivors with a residual tumor (36 direct extensions of tumor, 3 clumps of cancer cells in parabronchial tissues and 5 CIS), with an overall 5 yr survival of 34%. This data was found as consistent with the overall survival of their whole group of 1069 resected cases (48% in stage I, and zero in stage III). Diagnosis of residual bronchial tumor was always postoperative, while adjuvant RT was a routine treatment which resulted to improve the overall survival. Bronchopleural fistulas developed in 13.6% of cases.

Kaiser L.R. et al. In 1989 (23), reported on 45 cases of microscopic extramucosal residual tumors in both submucosal lymphatics and in peribronchial soft tissues. Intraoperative frozen section examinations upon the resected bronchial margins were done in all except 9 patients, but it failed in 41.7%. It means that 15 out of the 36 assessed patients weren't recognized in time and only subsequently found to have residual disease. Recurrent disease developed in 81% of cases with 32% local, and the majority at the bronchial stump. Moreover, the local recurrences were prevalent (60%) in N0 patients. Overall median survival was 15 months.

Liewald et al. in 1992 (24), reported on 21 cases of microscopic residuals in both mucosal and extramucosal bronchial margin. Frozen sections examination resulted false negative in four patients out of the 8 who were intraoperatively assessed, while in another four, who were erroneously thought to have an adequate margin and left without examination, the residual tumor was discovered postoperatively. Extramucosal microscopic tumors fared worse (median 9 months) than the mucosal ones (median 26 months) with an overall median of 12.1 months. Tumor stage was the most important factor of prognosis. Stages I and II fared better without microscopic residual than with it (median 64 and 21 months for Stage I, while 38 and 12 months for Stage II) and, overall, they fared better than the stage III group (median 9 months). In stage I and II, local recurrence appeared to be the main responsible for the deaths even though the majority of patients (18/21) had been treated by adjuvant RT.

Gebitekin et al. in 1994 (25), reported on 40 cases all revealed postoperatively following both a negative intraoperative assessment or no assessment, since the frozen section was requested only when the tumor was seen close to the bronchial margin. There were 5 submucosal lymphatic and 35 peribronchial tissues infiltrations. Recurrences were local in 58.5% and distant in 27.5%. The overall 5yr survival without and with positive margin was of 32% and 21.6% respectively, while it was of 52% and 40.8% in stage I and of 37% and 27.7% in stage II tumors. Therefore, since no statistical difference was found while comparing the survival data according to the stage, Authors conclude that microscopic residual tumors do not affect survival in stages I and II. Adjuvant RT, applied only for positive stumps in N0 or N1 cases, didn't appear to improve survival.

In the experience of Tan et al. in 1995 (26), 18

microscopic invasive tumors (5 mucosal and 13 extrachondral), 6 CIS and 5 cases of displasia at the resection line are reported. Overall mean survival was of 32.6 months for the invasive tumor group while it was of 41.7 months ( $p = 0,0004$ ) for the control group without tumor. Mean survival of CIS was consistent with that of control group, while it was of 29.1 months for mucosal tumors, and 11 months for the extrachondral ones. Intriguingly, 40% of cases with invasive tumors, both mucosal and extrachondral, resulted still alive at the review date ( $\geq 46$  months postoperatively). CIS was confirmed not to affect survival.

Snijder et al. in 1998 (27) in a retrospective study upon a relevant group of 834 resected Stage I NSCLC patients, registered 802 complete resections and 28 microscopic residuals at the bronchial margin (12 CIS, 8 mucosal and 3 peribronchial), there including 5 cases which were operated twice with a salvage intent (1 CIS, 3 mucosal, 1 mucosal+peribronchial). Diagnosis resulted basically on the specimens. Disease recurred in 48.5% of the 782 evaluable completely resected patients, with 30.7 local and 17.7% distant, while it recurred in 72.7% of the 22 evaluable cases of residual tumor group, with 54.5% local and 13.6% distant. Particularly for the CIS, recurrence was of 75% (9/12) with 55.5% local (5/9). Overall 5yr survival was 40% in the 5 patients who were operated twice, and 43% in the other 23 of residual group, with, respectively, 27.3% in mucosal and peribronchial residual tumors, and 58% in CIS. Therefore, while considering that the overall 5yr survival of the complete resection group was 54%, residual CIS, in spite of the high rate of local recurrence, couldn't be thought to affect survival in resected stage I tumors. Adjuvant RT demonstrated not to improve survival in patients with residual tumor and its clinical value remained unclear.

Ghiribelli et al. in 1999 (28), reported on 47 cases with 30 extramucosal, and 17 mucosal residual tumors all confirmed postoperatively, since even the 9 frozen section examination done, were partly false negative and partly no determinant. 17 patients received adjuvant RT, but no any improvement of survival was registered. Among the 19 patients followed up in more detail, there were 11 local recurrences and 8 distant. Median survival of the whole group was 22 months. Systematic frozen section examinations, reoperation only in stage I and II disease and adjuvant RT only as a choice in N2 cases, are recommended.

Barnes in 2000 (29), underlined the common thought that CIS doesn't affect spontaneous survival, while Massard et al. (30), applying the R classification of UICC (31), coded as "bronchial R1" the microscopically positive margin in 40 patients (20 CIS, 5 invasive mucosal, and 15 peribronchial), all found retrospectively. In none of these patients the intraoperative assessment had been done, since the resection was thought to be complete. Tumors recurred in 24 patients (60%) with 57.5% local (47.5% as local progression of the bronchial remnant and

10% as isolated local recurrence), 30% distant as metastatic spread, and 7.5% as combined local and distant. Almost all patients underwent adjuvant RT and, even though some therapeutic effects could be admitted, actually, 7 out 10 cancer-unrelated deaths there registered, were due to respiratory complications of RT. Spontaneous

overall 5yr survival was 38% in CIS (median 61 months), 20% in peribronchial tumors (median 18 months), while those called as “invasive mucosal tumors” survived less than 17 months. Again CIS resulted not to influence survival in itself, while adjuvant RT showed a clear adverse impact on survival (Table I).

Tab. I – REPORTED SPONTANEOUS LONG-TERM SURVIVALS FOR SOME MICROSCOPIC RESIDUAL TUMORS DISCOVERED AT THE BRONCHIAL RESECTION MARGIN

| <i>Authors and reference No ( )</i> | <i>Year</i> | <i>Positive cases No. of cases discovered in the total operated and % rate ( )</i> | <i>Site or histology</i>                                  | <i>5 yr survival No. of cases in the total discovered and % rate ( ), or only the % rate</i> | <i>Residual survivals</i>           | <i>Adjuvant therapy</i>              |
|-------------------------------------|-------------|------------------------------------------------------------------------------------|-----------------------------------------------------------|----------------------------------------------------------------------------------------------|-------------------------------------|--------------------------------------|
| Habein et al. (10)                  | 1956        | 18/631 (2.8%)                                                                      | Inadequate margin<br>Mucosal “metaplasia”<br>N1 proximity | ===                                                                                          | 2 years as the maximum lenght       |                                      |
| Groves et al. (12)                  | 1962        | 2                                                                                  | 2 Sq cell Carcinoma                                       | 2                                                                                            |                                     | Repeated local palliative treatments |
| Hughes et al. (13)                  | 1966        | 18/288 (6.2%)                                                                      | 1 Mucosal                                                 | 1/18 (5.5%)                                                                                  |                                     | CHEMO                                |
| Jeffery (14)                        | 1972        | 18/633 (2.8%)                                                                      | 5 Mucosal<br>1 Peribronchial<br>N1 in 3                   | 6/18 (33%)                                                                                   |                                     | RT                                   |
| Shields (9)                         | 1974        | 67/2371 (2.8%)                                                                     | 9 Submucosal (not lymphatics)                             | 9/67 (13.4%)                                                                                 |                                     |                                      |
| Soorae et al. (15)                  | 1979        | 64/434 (14.7%)                                                                     | 7 Direct extension<br>1 Parabronchial<br>7 CIS            | 15/64 (23.4%)                                                                                |                                     | RT<br>not routinary                  |
| Law et al. (16)                     | 1982        | 64/1000 (6.4%)                                                                     | 9 Direct extension<br>1 Submucosal lymphatics<br>6 CIS    | 16/64 (25%)                                                                                  |                                     |                                      |
| Heikkila et al. (22)                | 1986        | 44/1069 (4.1%)                                                                     | 36 Direct extension<br>3 Parabronchial<br>5 CIS           | 34% overall<br>(48% for stage I)                                                             |                                     | RT                                   |
| Kaiser L.R. et al. (23)             | 1989        | 45/2890 (1.6%)                                                                     | 9 Submucosal lymphatics<br>36 Peribronchial               | ===                                                                                          | Median 15 months                    |                                      |
| Liewald et al. (24)                 | 1992        | 21/805 (2.6%)                                                                      | 8 Mucosal<br>13 Extramucosal                              | ===<br>===                                                                                   | Median 26 months<br>Median 9 months | RT                                   |
| Gebitekin et al. (25)               | 1994        | 40/735 (5.4%)                                                                      | 5 Submucosal<br>35 Peribronchial                          | 21.6% overall lymphatics                                                                     | (40% for Stage I, 27% for Stage II) | RT                                   |
| Tan et al. (26)                     | 1995        | 18/255 (7%)                                                                        | 5 Mucosal<br>13 Extrachondral                             | ===<br>===                                                                                   | Mean 29.1 months<br>Mean 11 months  |                                      |
| Snijder et al. (27)                 | 1998        | 28/834 (3.3%)<br>(only Stage I resected NSCLC)                                     | 11 Mucosal<br>4 Peribronchial<br>12 CIS                   | 43% overall<br>(27% for mucosal and peribronchial 58% for CIS)                               |                                     | RT<br>Unclear value                  |
| Ghiribelli et al. (28)              | 1999        | 47/1384 (3.4%)                                                                     | 17 Mucosal<br>30 Extramucosal                             | ===                                                                                          | Median: 22 months                   | RT as a choice                       |
| Massard et al. (30)                 | 2000        | 40/ (<2%)<br>R1                                                                    | 15 Peribronchial<br>5 Mucosal<br>20 CIS                   | 20 % overall<br>===<br>38% overall                                                           | Median <17months                    | RT<br>7 RT-related deaths            |

Tab. II – SUGGESTED SAFE LENGTHS AND RULES FOR THE RESECTED DISTAL BRONCHUS

| Authors and reference No. | Year | *MSD (mm) | Rules                                                                                         |
|---------------------------|------|-----------|-----------------------------------------------------------------------------------------------|
| Habein et al. (10)        | 1956 | 15.00     |                                                                                               |
| Cotton (11)               | 1959 | 19.00     |                                                                                               |
| Soorae et al. (15)        | 1979 | 15.00     |                                                                                               |
| Law et al. (16)           | 1982 | –         | A complete bronchial ring distal to the bronchial division, must be intraoperatively assessed |
| **Kaiser K. et al. (33)   | 1993 | 20.00     |                                                                                               |
| Kara et al. (32)          | 2000 | 15.00     |                                                                                               |

\*Minimal Safe Distance from the proximal limits of tumor

\*\*Randomized Study.

Kara et al. (32), recently suggested to move back to cm 1.5 the safe length for any resected distal bronchus since, through a well designed pathologic study upon specimens, it resulted to assure a clear margin in over 90% of the cases. However, this data seems not to consider the previous one obtained by K. Kaiser et al in 1993 (33), through a formally prospective design, where only a safety distance of >20 mm demonstrated to assure a clear margin in over 95% of cases (Table II).

As far as the second surgical target is concerned, *the long-lasting surgical experience with the mediastinal lymphadenectomy*, has taught that any microscopic positive margin left there behind represents a hopeless failure, while distant metastases are the most frequent site of recurrence and, eventually, the cause of death. Really, the anatomical microvasculature of the lymphatic network seems to prevent the surgical clearing of being complete in almost all cases. According to the historical data (34, 35, 36, 37, 38), the majority of operated N2 follow their own natural course, with final 5yr survival rates ranging from 9 to 30%, and the last peak exclusively ascribed to a minor subgroup with *limited N2 disease*.

In such a specific field, two modern european contributions are worthy mentioning.

Riquet et al. in 1995 (39) reported on 237 NSCLC with N2, where all the hilar-mediastinal lymph nodes were removed through a systematic dissection and carefully classified. The mediastinal lymphatic area was thought completely cleared because the 30 cases of microscopic positive margin, all found on the specimens in spite of the negative frozen sections examination, were extra-mediastinal.

A single lymph nodes chain was involved in 141 cases, two chains in 72 and three or more in 24; N2 disease would have been missed in 45 cases of single chain involvement if a complete mediastinal lymphadenectomy had not been performed. Distant metastases were the preminent site of recurrence, while survival was significantly better when a complete lymph node dissection

was achieved (20.1% vs. 8.3%, 5yr), with the best rate in patients found with a single level involved (26.3%). Izbicke et al. in 1994 (40) and in 1998 (41), reported on their results with a randomized study upon 182 NSCLC with N2, where the systematic hilar/mediastinal lymphadenectomy was compared to the lighter lymph node sampling, while the cancer-related survival was the main target. Although no statistical difference in survival was found in both the intermediate (26.8 months) and final end points (47 months), a subgroup of patients with “limited N2 disease” appeared to clearly benefit in survival from the systematic lymphadenectomy (median 47 months).

The Naruke’s updated report of 1997 (42), with a 17.4% overall 5yr survival upon 546 completely resected patients including N2, confirms the still unmodified critical situation of N2 patients today: this controlled data represents in fact only a minor improvement when compared to the 13.8% 5-yr survival obtained upon the historical group of the first 421 patients operated in the same Institution (35).

Therefore, while considering this unfavourable condition, one cannot help thinking to the recent positive results obtained by some Japanese groups upon the newly recognized class of early detected, minute, stage I NSCLC with N2, who underwent a complete resection through the systematic hilar/mediastinal dissection.

In a series of 337 early detected small peripheral tumors, Asamura, Naruke et al. reported, in 1996 (43), a rate of 11.5% N2 for tumor sizes <2.0 cm, while it was of 21.5% for sizes of 2-3 cm.; the 5yr survival after the complete resection was of 44.5%.

Watanabe in 1996 (44), reported a rate of 15% N2 in tumors of 11-20 mm, while it was of 24% in tumors of 21-30 mm. The 5yr survival in this group showing a true clinically-latent N2, was of 33%. In a comparable series of small cancers, Tateishi reported, in 1995 (45), a rate of 19% N2 and a 5yr survival of 30%.

These results with 5yr survivals ranging from 30 to 45% represent indeed, a true challenge when compared with the historical ones of surgery for N2. Moreover, the clinical evidence of such highly competitive survivals, gives definitively rise not only to the curative effect of the systematic lymph node dissection, but, also, to its diagnostic power. It clearly appears when the complete hilar-mediastinal lymph node dissection is performed upon the clinically apparent T1N0 stage I NSCLC, where the suspicion of an already present N2 is banished by the usually expected limited tumor progression.

## Discussion

Data is collected from all retrospective reports except one (31).

The positive resection margin and the local recurrence are studied through the clinically significant figures of *the*

*microscopic residual tumor at the bronchial resection margin and the critical resection margin within the ipsilateral mediastinal lymphatic area.* Such figures are consistent with the Izbicki (41) and Lacasse (46) reports, and, although largely different in their anatomic-clinical aspect and yet unconfirmed in their prognostic significance (46), they appear as well to give further insights to the matter of *microscopic incomplete vs complete resection.*

As to the first figure, it is known that any "microscopic positive margin" is a powerful negative factor of prognosis together with the "higher stage of disease" (2). In the mean time, the bronchial resection line appears to be the single most frequent site of recurrence (16%) in the resected lower Stage I and II NSCLC (3). This latter data is now receiving further support by the updated experience of Snijder et al (27), with a rate of 30.7% local recurrence in 782 completely resected stage I NSCLC, and a rate of 54.5% in the cases with microscopic bronchial residual tumors. A whole additional support comes also from the review (10, 23, 24, 25, 28), with a range of 32% to 58.1% local recurrences, and, in one instance (23), the report that the majority of them were at the bronchial stump. On the other hand, a microscopically positive bronchial margin is reported with a relative low rate of 2% to 14.7%, according to the postoperative assessment (30, 9, 14, 16, 22, 24, 25, 26, 27, 28, 15), while the rate of the intraoperative assessments resulted even lower. Such an evident discrepancy is clearly connected with both the low indication to the frozen sections examination registered, and the low accuracy of the method due to the number of false negatives reported (22, 23, 24, 25, 27, 28, 30, 40). Therefore, while relating the high rate of local recurrence at the stump to the low intraoperative diagnostic yield, the surgical evidence of an inadequate approach to the bronchial resection margin, arises directly. Moreover, a correlation does also exist between the high rate of local recurrence (32% to 58.1%) and the basically underestimated number of microscopic residuals at the bronchial margin. Accordingly, the clinical evidence of a direct responsibility of these latter in determining the bronchial relapse, can be admitted.

CIS, mucosal carcinoma and extramucosal carcinoma in both submucosal lymphatic and peribronchial soft tissues are the common pathologic findings, with squamous cell and adeno carcinoma as the most frequent histology, and the higher clinical malignancy recognized to the last two extramucosal subsets.

On the other hand, these microscopic tumors, although representing a failure for the surgical attempt for cure, can be even followed by a spontaneous prolonged survival. This seems to prevail in those growing strictly within the mucosal layer, taken for granted the low stage of primary tumor (9, 14, 15, 16, 26, 27, 29, 30). It means a median survival of 26 to 29,1 months compared with the 9 to 22 months of the extramucosal residuals (23, 24, 26, 27, 28, 30). CIS has constantly shown not to influence survival, but the demonstrated tendency to metastasize (16) or to

recur (27), urgently requests to learn thoroughly about its biological behaviour. Mucosal tumors also need to be fully identified in the morphologic aspects of their invasive tendency. Moreover, the indiscriminate use of "mucosal" and "mucosal invasive" definitions (28), and the tendency to cumulate the survival of mucosal and extramucosal tumors (25, 26), makes it rather difficult to reach conclusions on the spontaneous survival of such microscopic residual tumors. Therefore, it mustn't be surprising if these uncertainties could still give rise to Law's skepticism! (16).

In this ambit, the advanced Japanese research upon the RX-occult hilar tumors (ROC) (47), could surely be of some help. Indeed, in such a family of minute mucosal tumors of proximal bronchi to whom CIS also belongs, the biological behaviour appears rather different than the macroscopic NSCLC. They are inherently indolent and more slowly growing (48), while the reversibility of bronchial cell atypia has also been demonstrated to occur spontaneously or after smoking cessation (49, 50). In addition it has been demonstrated that the regression of some molecular abnormalities usually predict the regression of CIS to a lower grade lesion (51), while Nagamoto et al. (52) morphologically differentiated the slowly growing "creeping type" from the more aggressive "penetrating type" of mucosal tumors.

Therefore, transferring this specific knowledge to the field of residual mucosal tumors at the bronchial resection margin, it will probably help pathologists to read the morphologic aspects of their biologic tendency to invade, better. The microscopic extramucosal tumors, instead, are to be definitively considered no different from the "macroscopic NSCLC" (48).

From the clinical viewpoint, when the microscopic residual is discovered intraoperatively, a further bronchial resection represents the ideal approach, provided that the modified anatomy and the surgical skill allows to do it. When, instead, the diagnosis is delayed until the pathologic assessment, a second operation (salvage operation) can still be planned, but the indication now is ruled by the additional risk of a completion major resection, as well as the psychologic availability of patients and the lower stage of primary tumor (23, 27, 28, 30). Stage III patients are in fact excluded from this chance. As for the CIS the second operation is not universally accepted yet (30).

Finally, the role of adjuvant RT in improving survival as a single treatment, has not yet been conclusively demonstrated (24, 25, 27, 30) in line with PORT analysis (53), with only one assenting position registered in our review (22). However, the results of a recent randomized study on the effect of RT in preventing local recurrence at the bronchial stump in cases of staged Ia and Ib NSCLC (54), clearly support the therapeutic efficacy of the treatment. Indeed, a part from the total absence of RT-related complication and/or mortality, a significant protective effect against the local recurrence was demonstrated.

As to the second figure of *critical resection margin within the ipsilateral mediastinal lymphatic area*, the experience already acquired with the systematic lymph node dissection, allows us to recognize that a safe surgical margin for a complete local control, cannot be always assured in this area, basically due to the less definite microvascular lymphatic boundaries.

The contributions by Riquet (39) and Izbicki (40, 41), have widely confirmed the role of the systematic lymph node dissection in improving the diagnostic accuracy upon the N status, and the completeness of resection of Stage III NSCLC with N2, while the possibility to find more patients with a limited N2 and better survival, really increases.

Of particular interest appears the matter of the early detected, minute NSCLC with N2 (43, 44, 45). Actually, either the diagnostic power in detecting N2 disease even in stage I NSCLC, and the curative power of the systematic nodal dissection when it is performed in time, have been pointed out. In addition, the advanced clinical information about the heterogeneous pattern of metastatic mediastinal lymph node status and the closely connected differences in prognosis upon treatment (55), let us reasonably think that even the overall prognostically negative N2 disease, could be clinically handled better, while the systematic mediastinal lymphadenectomy will gain a further prognostic quality.

## Conclusions

The complete resection results from a surgical approach which has helped to completely remove any M0 NSCLC together with the local-regional spread (N1-2, T3, T4). In other words, it directly addresses to the curativity of complete resection.

The microscopic residual tumor at the bronchial resection margin as well as the critical resection margin within the ipsilateral mediastinal lymphatic area, represent the clinical concern about the microscopic incomplete vs. complete resection, properly.

As for the *microscopic residual tumor at the bronchial resection margin*, it can be considered for surgery only when the primary tumor is staged I or II since the expected longer survival after resection makes the risk of a second operation cost-effective.

If detected intraoperatively, the positive bronchial margin could represent, at times, a technical problem, but it always becomes an ethical problem when discovered postoperatively, considering that as few patients as possible should be denied the second operation.

From this study, the bronchial resection margin has resulted overall underestimated for reasons which appear surprisingly as less relevant as easy to modify. Accordingly, the common surgical sense would recommend special diagnostic attention upon the bronchial margin as well as a true personal availability to perform an otherwise tedious

and time-consuming repeated frozen sections examination. On the other hand, a direct responsibility of the microscopic bronchial residual in determining the local relapse, shared, at least, with T2 and N1 factors, clearly results from the review. Finally, prospective clinical researches are requested with the aim to clarify the still obscure points on the spontaneous survival.

As for the *critical resection margin within the ipsilateral mediastinal lymphatic area*, the recognized unmodifiable power of N2 disease in affecting prognosis, is the most relevant aspect of the problem.

The important contributions of Riquet (39) and Izbicki (40, 41) have confirmed that it is possible to assure, by the systematic lymph node dissection, not only a complete resection of all the lymph node groups but also an improvement of the staging accuracy through a suitable "stage migration", due to the discovery of some positive nodes that would not have been routinely sampled. Moreover, the discovery of those minor groups with a "limited N2" and an expected better survival, is also assured. Therefore, improving the recognition of both the minute NSCLC with N2, and the cases with still "limited N2" through this extended procedure, appears as the confirmed surgical approach to the N2 disease, nowadays. This surgical rationale is obviously open to the combined treatment protocols whenever a clinically evident or a bulky N2 have to be treated. In the meantime, the advanced prognostic criteria based upon the newly assessed heterogeneous pattern of N2 (55), will surely help in deciding the most appropriate combination of induction therapy protocols.

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