Editorial

Complete Resection in Non-small Cell Lung Cancer Surgery

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Complete resection for the local control of non-small cell lung cancer (NSCLC) strictly depends on the surgical clearance of two ancillary components of the tumor: 1) the resection margin left behind the removed primary growth and 2) the satellite lymphatic sump drain system which represents the anatomical next step for the tumor progression towards the mediastinal lymphatic area. Indeed, any undiscovered microscopic residual lying within these surroundings is expected to negatively weigh upon the prognosis, as well as any other gross residual does.[1)] Local recurrences, very often arising directly from the microscopic remnant, and distant metastases, are the main clinical concerns following incomplete resection.

On clinical grounds, these issues directly address two major problems which present differently, according to the different origins of their own determining factors.

On one hand, there are the recurrences which largely affect the survival of resected Stages I and II NSCLC, with rates of 20 to 47% in Stage I, and of 45 to 62% in Stage II, respectively. Actually, besides the recognised negative prognostic influence of T2 and N1 factors, unrecognised microscopic remnants at the bronchial resection margin or anywhere within the ipsilateral hemithorax, could be thought to share the responsibility of worsening the prognosis in these otherwise apparently completely resected lower stage NSCLC.

On the other hand, there is the problem of tumoral progression within the mediastinal lymphatic area (N2 disease), where long surgical experience with systematic mediastinal lymphadenectomy, has taught us that any microscopic positive margin left behind represents a hopeless failure. Anatomical conditions of the lymphatic bed or a still silent systemic spread prevent the surgical clearing being oncologically complete in almost all cases.

The microscopic residual tumor at the proximal bronchial resection margin, although representing an incomplete resection, can even be followed by a spontaneous prolonged survival and, because of this apparent contradiction, the issue of complete resection resulted initially somewhat confused.

However, in the 70s, T.W. Shields tried to organise this whole matter presenting, in 1974,[2)] the first nine cases of microscopic residual infiltration of submucosal (non lymphatic) bronchial layer, with a demonstrated long survival (Table 1). He offered, at the same time, a concrete definition of "complete resection" by focussing on the opposite condition of "incomplete resection", which has to be exclusively based upon the histological proof of a residual microscopic tumor in the ipsilateral hemithorax. He also decided to deny any credibility to the subjective feeling of surgeons in judging the tumor clearance at the resection margin by the naked eye. Finally, he identified three main targets for ipsilateral residual microscopic disease: the mediastinal tissue and lymph nodes, the parietal pleura and chest wall, and the proximal bronchial resection margin. The first and the last one have become the top representatives of "incomplete resection", based on extensive clinical attention and the number of scientific contributions devoted to the subject over the years.

Analysis of clinical reports on the positive bronchial resection margin (Tables 1, 2) has largely confirmed the characteristic features of prolonged postoperative survival, with 5-year rates ranging from 14 to 43% (16.4% in Shields' data). A series of related prognostic factors have also been recognised, with the more favourable lower Stage I disease, carcinoma in situ (CIS) histology and the mucosal location of tumor, and negative ones, such as peribronchial infiltration, lymphangiosis carcinomatosa, and higher stage of disease. A negative influence on the surgical approach in general, due to an average low diagnostic accuracy, has also been noticed, and it evidently resulted from the continuing tendency of surgeons to make a "naked-eye" evaluation of the margin, the consequent low employment of the crucial intraoperative frozen-section examination, and also, by the high rate of false negatives due to the frequent improper methodological appli-

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Table 1. Historical reports on microscopic residual tumors at the bronchial resection margin

Authors	Year	Total no. of local microscopic residual tumors in the total operated pts (%)	Number, site or histology of microscopic residual tumors at the bronchial resection margin	5-yr spontaneous survival No. of cases in the total discovered and % rate, or only the % rate	Residual survival	Adjuvant therapy
D.F. Griess[1]	1945	13/30 (43.3%) Pathologic study upon "old fixed" specimens 13 proximal direct extension				
H.C. Habein[2]	1956	18/631 (2.9%) Clinical and pathologic study 18 proximal direct extension			Up to 2 years	
R.E. Cotton[3]	1959	82/100 (82%) Pathologic study upon "freshly fixed" specimens 82 proximal direct extension				
L.K. Groves[4]	1962	2	2 recurrences at the bronchial stump	2		Repeated local treatments
R.K. Hughes[5]	1966	18/288 (6.3%)	4 submucosal lymphatic 1 mucosal	1/18 (5.6%)		Chemo
R.M. Jeffery[6]	1972	18/633 (2.8%)	5 mucosal 1 peribronchial	6/18 (33.3%)		RT
T.W. Shields[7] T.W. Shields[7a]	1974 1989	221/2,371 (9.3%) 67 bronchial (12 gross residual)	24 peribronchial 31 submucosal (non lymphatics)	1 8 9/55 (16.4%)		
A.S. Soorae[8]	1979	64/434 (14.7%)	34 direct extension 14 lymphatic permeation 6 parabronchial 10 CIS	7 1 7 15/64 (23.4%)		RT not routinely
N. Roeslin[9]	1982	11/1,223 (0.9%)	11 recurrences at the bronchial stump	>10%	Median 36 mos	RT not routinely
M.R. Law[10]	1982	64/1,000 (6.4%)	26 mucosal 18 peribronchial 8 submucosal lymphatics 9 CIS	9 1 6 16/61 (26.2%)	2-yr survival 2/18	
L. Heikkila[11]	1986	44/1,069 (4.1%)	36 direct extension 3 parabronchial 5 CIS	34% overall (48% for Stage I)		RT routinely
L.R. Kaiser[12]	1989	45/2,890 (1.6%)	9 submucosal lymphatics 36 peribronchial	===	3-yr survival 20% overall Median 15 mos	RT almost routinely
G. Verleden[13]	1990	10/295 (3.4%)	10 recurrences at the bronchial stump (occult nodal invasion)		Median after surg 19.5 mos Median after recur 7.5 mos	Chemo - n. 2 RT - n.2 Redo - n. 2 None - n. 4

1) J Thorac Surg 1945; 14: 362–68. 2) J Thorac Surg 1956; 31: 703–17. 3) Br J Dis Chest 1959; 53: 142. 4) J Thorac Cardiovasc Surg 1962; 44: 385–91. 5) Ann Thorac Surg 1966; 2: 102–5. 6) Ann R Coll Surg Engl 1972; 51: 55–9. 7) Surg Gynecol Obstet 1974; 139: 569–72. 7a) Ann Thorac Surg 1989; 47: 487–8. 8) J Thorac Cardiovasc Surg 1979; 78: 175–80. 9) Ann Chir Thorac Cardiovasc 1982: 36: 107–10. 10) Thorax 1982; 37: 492–5. 11) Ann Chir Gynecol 1986; 75: 151–4. 12) Ann Thorac Surg 1989; 47: 265–9. 13) Eur Respir J 1990; 3: 97–100.

pts, patients; yr, year; chemo, chemotherapy; RT, radiotherapy; CIS, carcinoma in situ; mos, months; surg, surgery, recur, recurrence; n., number

Table 2. Modern reports on microscopic residual tumors at the bronchial resection margin

Authors	Year	Total no. of local microscopic residual tumors in the total operated pts (%)	Number, site or histology of microscopic residual tumors at the bronchial resection margin	5-yr spontaneous survival No. of cases in the total discovered and % rate, or only the % rate	Residual survival	Adjuvant therapy
F. Liewald[1]	1992	21/805 (2.6%)	8 mucosal 13 peribronchial	=== ===	Median 26 mos Median 9 mos	RT
K. Kayser[2]	1993	20/120 (16.7%) Pathologic study upon "frozen" and "freshly fixed" specimens 20 proximal direct extension				
C. Gebitekin[3]	1994	40/735 (5.5%)	5 submucosal lymphatics 35 peribronchial	21.6% overall (40% for Stage I, 27% for Stage II)		RT in 37.5%
H. Kimura[4]	1994	38/858 (4.4%)	38 bronchial remnant	35.6 overall (49% for Stage I)		RT routinely
K.K. Tan[5]	1995	18/255 (7.1%)	5 mucosal 13 extrachondral	=== ===	Mean 29.1 mos Mean 11 mos	
H.Dienemann[6]	1997	88/2,464 (3.6%)		===	Median 16 mos	RT in 50% of cases
H. Wertzel[7]	1998	3/338 (0.9%)	2 bronchial margin	===	===	===
R.J. Snijder[8]	1998	23/834 (2.8%) (only Stage I resected NSCLC)	8 mucosal 3 peribronchial 12 CIS	43% overall (27% for mucosal and peribronchial, 58% for CIS)		RT unclear value
C. Ghiribelli[9]	1999	47/1,384 (3.4%)	17 mucosal 30 extramucosal	===	Median 22 mos	RT as a choice
G. Rocco[10]	1999	41/1,689 (2.4%)	38 mucosal 3 peribronchial	18% overall	Median 17.5 mos	RT almost routinely
G. Massard[11]	2000	40/ (<2%) R1 disease	15 peribronchial 5 mucosal 20 CIS	20.0±10.3% === 38% overall	Median 18 mos Median 31mos	RT routinely 7 RT-related deaths
M. Mezzetti[12]	2001	43/2,350 (1.8%) (16 excluded after a completion redo)	21 mucosal 6 peribronchial		3-yr survival 29% overall	RT in 35% of cases
B. Passlick[13]	2001	54/1,162 (4.6%) R1 status as an "advanced disease" when LC is in present	22 lymphangiosis carcinomatosa (LC) (40.7%) 32 no LC	=== 20% overall	Median 13.3 mos Median 20.1 mos (49 mos for Stages I and II)	RT effective only in 25 no LC pts (median 23.3 mos)
H.S. Hofmann[14]	2002	26/596 (4.4%)	15 peribronchial (13 N2) 6 submucosal lymphatics (3 N2)	14% overall	N2 median 6 mos N0/N1 median 39 mos	RT (in 15 N2 median survival 14 mos)

1) J Thorac Cardiovasc Surg 1992; 104: 408–12. 2) Thorac Cardiovasc Surg 1993; 41: 308–11. 3) Eur J Cardiothorac Surg 1994; 8: 339–44. 4) Lung Cancer 1994; 11: 229–42. 5) Thorax 1995; 50: 4379. 6) Chirurg 1997; 68: 1014–9. 7) Thorac Cardiovasc Surg 1998; 46: 365–9. 8) Ann Thorac Surg 1998; 65: 212–6. 9) Eur J Cardiothorac Surg 1999; 16: 555–9. 10) Arch Chir Thorac Cardiovasc 1999, 21: 15–20. 11) Eur J Cardiothorac Surg 2000; 17: 557–65. 12) Minerva Chir 2001; 56: 1–6. 13) Ann Thorac Surg 2001; 72: 1160–4. 14) Eur J Cardiothorac Surg 2002; 21: 606–10.

pts, patients; yr, year; mos, months; RT, radiotherapy; CIS, carcinoma in situ

Table 3. Prevalent diagnosis and local recurrences rate in microscopic bronchial residual tumor

A - historical reports							B - modern reports					
No.	Authors	No. of cases	N	F	P	R	Authors	No. of cases	N	F	P	R
1	D.F. Griess	13			100% (RPD)		F. Liewald	21	13/21 (61.9%)	8/21 (38.1%); 4/8 FN (50%)	100%	
2	H.C. Habein	18			100% (RPD)	18	K. Kayser	20		100% pos	100% (PPD)	
3	R.E. Cotton	82			100% (RPD)		C. Gebitekin	40	100%	40 FN (100%)	100%	17 local (42.5%)
4	L.K. Groves	2			NM	2	H. Kimura	38	NM	NM	100%	
5	R.K. Hughes	18			100%		K.K. Tan	18	NM	NM	100%	
6	R.M. Jeffery	18			100%		H. Dienemann	88	NM	Recommended	NM	
7	T.W. Shields	55			100%		H. Wertzel	3		3 FN (100%)	100%	
8	A.S. Soorae	64			100%		R.J. Snijder	23	NM	13 (56.5%)	100%	12 local (52.1%)
9	N. Roeslin	11			NM	11	C. Ghiribelli	47	38/47 (80.9%)	9/47 (19.1%); 4/9 FN (44.4%)	100%	11 local (23.4%)
10	M. Law	64		NM	100%		G. Rocco	41	39/41 (95.1%)	2/41 (4.9%) 1 TN	100%	4 local (9.8%)
11	L. Heikkila	44	100% neg	Recommended but not done	100%		G. Massard	40	NM	Not routinely	100%	7 local progr (17.5%)
12	L.R. Kaiser	45	9/45 (20%) neg	36/45 (80%); 15/36 FN (41.7%)	100%	11 local (24.4%)	M. Mezzetti	27	100%	Recommended but not done	100%	20 local (74.1%)
13	G. Verleden	10			NM	10 local	B. Passlick	54	100%	Not done	100%	NM
14							H.S. Hofmann	26		11/26 FN (42.3%)	100%	NM

N, "naked eye" margin; F, intraoperative frozen section examination; P, pathology on specimen; R, recurrences; RPD, retrospective full pathologic design; PPD, prospective full pathologic design; pos/neg, positive/negative; FN, false negative; TN, true negative; NM, not mentioned; progr, progression

cations (the extrabronchial tissues were usually not sampled) (Table 3). Therefore, it must not be surprising if the resulting underestimation of the real number of microscopic residuals, has greatly impaired the rate of complete resection in this specific surgical area. The registered high number of local recurrences (from 9.8 to 74.1%) strongly supports this assumption (Table 3).

As to the second representative surgical margin in the mediastinal lymphatic area, experience acquired along the years has clearly indicated that evaluation of completeness of resection there has to be considered to entail a high risk of failure, for the reasons already mentioned. According to the historical data,[3,4] the majority of apparently complete resected N2 cases follow their own course, with final 5-year survival rates ranging from 9 to 30%, and the peak exclusively ascribed to a small subgroup with the chance of limited N2 disease. A large cultural debate around the completeness of resection with the most distal (highest) mediastinal node when it is found positive for metastasis, is true after many years, and a final answer is still awaited. The last updated report of Naruke et al. in 2001,[5] presents an overall 5-year survival rates of 19.8% in a group of 736 apparently completely resected patients with N2, and, this data shows only a minor improvement when compared to the 13.8% 5-year survival rates obtained with the historical group of 421 patients.[4] However, the modern surgical tendency, based on the clinical data of Riquet et al.,[6] Izbicki et al.,[7] and more recently, Keller et al.[8] clearly supports systematic mediastinal lymphadenectomy for complete resection, aimed not only at a better staging of disease, but also at discovering as many patients as possible with limited N2 disease, and assuring them the best expectation for survival.

In conclusion, complete resection can be defined as the "histologically proven complete surgical clearance of any resectable M0 NSCLC" after Shields. It appears properly defined through the two already described clinical targets. However, that is only a static representation of a

matter which is quickly moving forwards, through incoming new knowledge on the "minimal residual disease". Actually, the newly proffered molecular diagnostic technologies[9] appear able to discover single occult tumor cells or clusters of cells in mediastinal lymph nodes otherwise considered tumor-free. Therefore, the present advances allow us to foresee how deep the boundaries of the "complete resections" should be moved in the near future for better local control of lung cancer.

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