Lung cancer: diagnosis and surgery

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Lung cancer is a major health problem due to its high incidence and poor curability. This disease is the most fatal cancer in the world and it is estimated that there have been over 1 300 000 lung cancer deaths in the year 2000 [1]. The enormous fatality rate reflects the limited chance of cure, with a dismal overall 5-year survival rate of approximately 14% in the United States. In Europe, over 90% of all cases diagnosed die within 5 years (Table 1). Two thirds of cases have advanced disease at diagnosis and the vast majority die of cancer despite aggressive multimodality management. Surgical excision is still the most effective way to achieve local control and permanent cure, but is only applicable to 25–30% of cases due to the tumour burden and tobacco-related comorbidity.

As in other solid tumours, long-term survival after complete resection is inversely related to the extent of disease, which is best expressed by pathological TNM classification. In this disease, the crucial role of staging is to separate the subset of patients that are amenable to curative surgery from those who can be better treated by chemo-radiotherapy or palliative management, and avoid unnecessary therapies as much as possible.

It appears from epidemiological trends that major reductions in mortality for this disease can only be achieved by early detection and truly innovative treatments. Selective intervention may offer a useful support to primary prevention in high-risk individuals. This is particularly true for the expanding cohort of former smokers, who remain at higher risk of lung cancer for at least 20 years. New research strategies are essential to reduce lung cancer mortality.

Table 1
Population-based survival (all incident cases) SEER data — EUROCARE (males 1983–1985)

Country	Survival (%) (5-year)	% resected
USA	14	25–30
Europe	8	
The Netherlands	13	
Italy	8	
United Kingdom	6	5–10

SEER = Surveillance, Epidemiology and End Results.

Early detection and screening

The prognosis of lung cancer depends largely on early detection and immediate treatment prior to metastatic spread. For Stage I lung cancer, the 5-year survival rate is now above 60% [2–4] and over 80% for tumours of less than 2 cm of diameter [5]. These data suggest that early detection and surgical treatment would have a huge beneficial effect on the lung cancer population.

In the past, a few large randomised studies have not shown any improvement in mortality among heavy smokers with repeated chest X-ray and sputum cytology. These four large trials being: the Memorial-Sloan Kettering Trial (MSKCC) [6], John Hopkins Study [7], the Mayo Clinic Study [8] and the Czech Study [9] were carried out in the 1970's and early 1980's.

Two of these trials had the same design (MSKCC and John Hopkins studies), comprising chest X-ray annually versus chest X-ray plus 3-day pooled sputum every four months, thus assessing only the value of sputum cytology. Results of these two studies showed no difference in lung cancer mortality in the 'dual screen' group [7,8]. The Mayo trial comprised four-monthly chest X-ray and sputum versus no screening (only initial prevalence screening with chest X-ray and sputum cytology), however, 50% of the controls did actually have annual chest X-rays which weakened the study and though the resectability rate was higher in the screened group (46% vs 32%) and the 5 year survival in this group 35% compared with 15% in the control group, there was no difference in the overall lung cancer mortality between the two groups [8]. The Czech study involved

chest X-ray and sputum cytology every 6 months for 3 years for the study group and no screening for the control group, but in the subsequent 6 year follow-up period both groups had annual chest X-rays and so the experimental design failed to detect any difference between the two initial screening regimes [9]. There were considerable flaws throughout all four studies especially with poor adherence to the protocols and the limited power of the National Cancer Institute (NCI) co-operative trials (these being designed to show a 50% reduction in lung cancer mortality with 80% power, but unable to demonstrate reductions in lung cancer mortality below this level). However, the seemingly negative results of these four large trials, in terms of no reduction in lung cancer mortality caused a worldwide cessation of any further development in programmes for the early detection of lung cancer for several years.

In more recent times, there has been a resurgence of interest in this field mainly due to the belief that early detection of lung cancer should reduce mortality for this disease. Given the significantly higher 5-year survival for cases resected in stage I compared with more advanced cases, and particularly after the advent of low dose spiral computed tomography (CT). Japan conducted two studies assessing the role of CT screening for lung cancer during the 1990's. Kaneko et al [10] compared low-dose spiral CT scanning with posteroanterior and lateral radiographs performed 6 monthly on a high-risk (for lung cancer) population. Fifteen cases of lung cancer were detected by spiral CT (out of 1369 high-risk individuals) and yet only 4 of them were detected by chest radiography. Fourteen of the fifteen lung cancers were stage I with an average diameter of just 16 mm, whereas the average diameter of cancers detected on chest radiography was 30 mm, thus highlighting the much improved sensitivity of this technique in terms of detecting small lesions [10]. A further Japanese study published in 1998 produced similar results with the detection of 19 lung cancers from a general population of 5483 with a mean detectable lesion size of 17 mm and of which 80% of the lung cancer cases were stage I [11]. In comparison, the 3 large American screening trials resulted in only 40% of detected lung cancers being stage I.

The recent Early Lung Cancer Action Program (ELCAP) publication reports the initial results of another study assessing low-dose spiral CT scanning as a means of detecting lung cancer in a high-risk population [12]. The baseline results (long-term follow-up not yet completed) are very similar to the Japanese studies with the detection of 27 cancers from 1000 high-risk individuals of which 85% were classified as stage I (Table 2). In comparison only 7 cancers were detected by chest radiography in the same population. Fifty-six percent of the detected cancers were 10 mm or less in diameter. In actual fact, 233 individuals (from the initial 1000) were found to have between one and six non-calcified nodules by spiral CT and all required further investigation to determine which were actually malignant (27 individuals in this case). The study protocol aimed to minimise the need for biopsies and invasive procedures [12].

Table 2
Results of the ELCAP study: diagnostic efficacy of spiral CT screening versus standard chest X-rays in 1000 heavy smokers

	Chest X-rays	Spiral CT
Non-calcified nodules	79	363
Pts. with nodules	68 (7%)	233 (23%)
Cancers	7 (0.7%)	27 (2.7)
Early stage	4	23 (85%)
Resectable		26 (96%)

Pts = patients; CT = computed tomography.

The ELCAP study has only reported the baseline results and although these are promising, so too were the initial prevalence results of the four large screening trials conducted twenty years ago. The long-term follow-up of the ELCAP malignant cohort will provide the curability and survival data which will ultimately indicate whether low-dose spiral CT scanning indeed reduces mortality from lung cancer. It is to be hoped that the high rate of detection of stage I, small localised cancers will allow surgical cure in many cases and thus increase survival and reduce mortality among the screened population.

In addition to improvement in CT scanning techniques, advances in immuno-cytological assessment of sputum may provide a more sensitive and accurate method of screening than present conventional sputum cytology and in addition to low-dose spiral CT scanning could form the framework for future screening programmes [13]. Moreover, new research experience has demonstrated that specific microsatellite alterations can be detected in the plasma DNA of patients operated upon for very small lung cancers [14], thereby offering a new prospect for early diagnosis to be combined with radiological assessment.

Clinical diagnosis and staging

Over 95% of lung neoplasms belong to the four main histological types: squamous cell carcinoma, adenocarcinoma, small cell carcinoma and large cell carcinoma [15,16]. The new World Health Organiza-

Table 3
Histopathological classification of lung cancer (WHO/IASLC, 1998)

I Epithelial	
Preinvasive	1 Squamous dysplasia and in situ cancer
	2 Atypical adenomatous hyperplasia
	3 Neuroendocrine cell hyperplasia
Malignant	(a) Squamous cell carcinoma
	Variants
	1 Papillary
	2 Clear cell
	3 Small-cell
	4 Basaloid
	(b) Small cell carcinoma
	Variant
	1 Combined small cell carcinoma
	(c) Adenocarcinoma
	1 Acinar
	2 Papillary
	3 Bronchioloalveolar carcinoma
	2 Solid adenocarcinoma with mucin formation
	3 Mixed
	(d) Large cell carcinoma
	Variants
	1 Neuroendocrine
	2 Basaloid
	3 Lymphoepithelioma-like
	4 Clear cell
	5 Rhabdoid phenotype
	(e) Adenosquamous carcinoma
	(f) Pleomorphic/sarcomatous carcinoma
	(g) Carcinoid tumour
	1 Typical
	2 Atypical
	(h) Carcinomas of salivary gland type
	1 Mucoepidermoid carcinoma
	2 Adenoid cystic carcinoma
	(i) Unclassified carcinoma

WHO = World Health Organization.

tion (WHO)/International Association for the Study of Lung Cancer (IASLC) classification is reported in Table 3.

The diagnostic work-up if lung cancer is suspected is outlined in Table 4. CT scan of the chest and upper abdomen represents the most accurate examination in the majority of patients. Widespread use of spiral CT scan has greatly improved the accuracy of clinical staging, although new problems of interpretation arise with increased sensitivity and detection of small satellite pulmonary nodules. Assessment of mediastinal nodes metastases is based essentially on size, and a cut-off of 1 cm in the maximum transverse diameters is usually selected to define suspicious nodes. With these criteria, the

Table 4
Suggested examinations if lung cancer is suspected

Initial clinical-diagnostic evaluation
- Physical examination
- Cell count and biochemistry
- Chest X-rays (2 projections)
- Chest CT scan
- Bronchoscopy
- Sputum cytology (3 days)

Pre-treatment staging
- Upper abdomen CT or ECHO
- Brain CT or MRI
- Mediastinoscopy for cN2 (or cT4) at CT scan
- Bone scan + X-rays (if positive scan)
- PET scan (if multiple lesions at CT)
- Needle aspiration cytology for pleural effusion
- Video-assisted thoracoscopy (if pleural cytology negative)
- Needle aspiration biopsy of any metastatic site

CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography.

probability of the diagnosis being false-positive is in the order of 10–20%, and being false-negative is 20–30%. The diagnostic accuracy of conventional sputum cytology can reach 80% for central lesions, but is only 20–30% for small peripheral tumours. Fibreoptic bronchoscopy is an essential complement of the radiological examination to collect proper samples under direct vision or radiologically-guided brushing/lavage and contribute to the assessment of optimal resection volume. Fine-needle aspiration biopsy is a valuable diagnostic procedure in peripheral lesions with negative cytology. It is accurate in achieving tissue diagnosis in 80–90% of cases, but is not always so for immunohistochemical analysis.

Screening of asymptomatic metastases with brain CT or magnetic resonance imaging (MRI) and bone scan has become part of routine clinical staging, even though the frequency of occult metastases may be very low in earlier stages.

Positron emission tomography (PET scan) is a new technology now providing a powerful functional tool to investigate nodal, as well as distant dissemination, and should be used, whenever available, to improve non-small cell lung cancer (NSCLC) staging or assess residual disease after induction therapy. PET scan has been applied to detect both mediastinal lymph nodes metastases (sensitivity 76% to 100%, specificity 81% to 100%) [17] and visceral metastatic disease [18]. In a recent article published in July 2000 [19], the authors adjusted for each other the results of PET and CT in the preoperative staging of NSCLC. Only PET results were positively correlated with the histopathological findings in mediastinal lymph nodes ($P < 0.001$), and the sensitivity and the

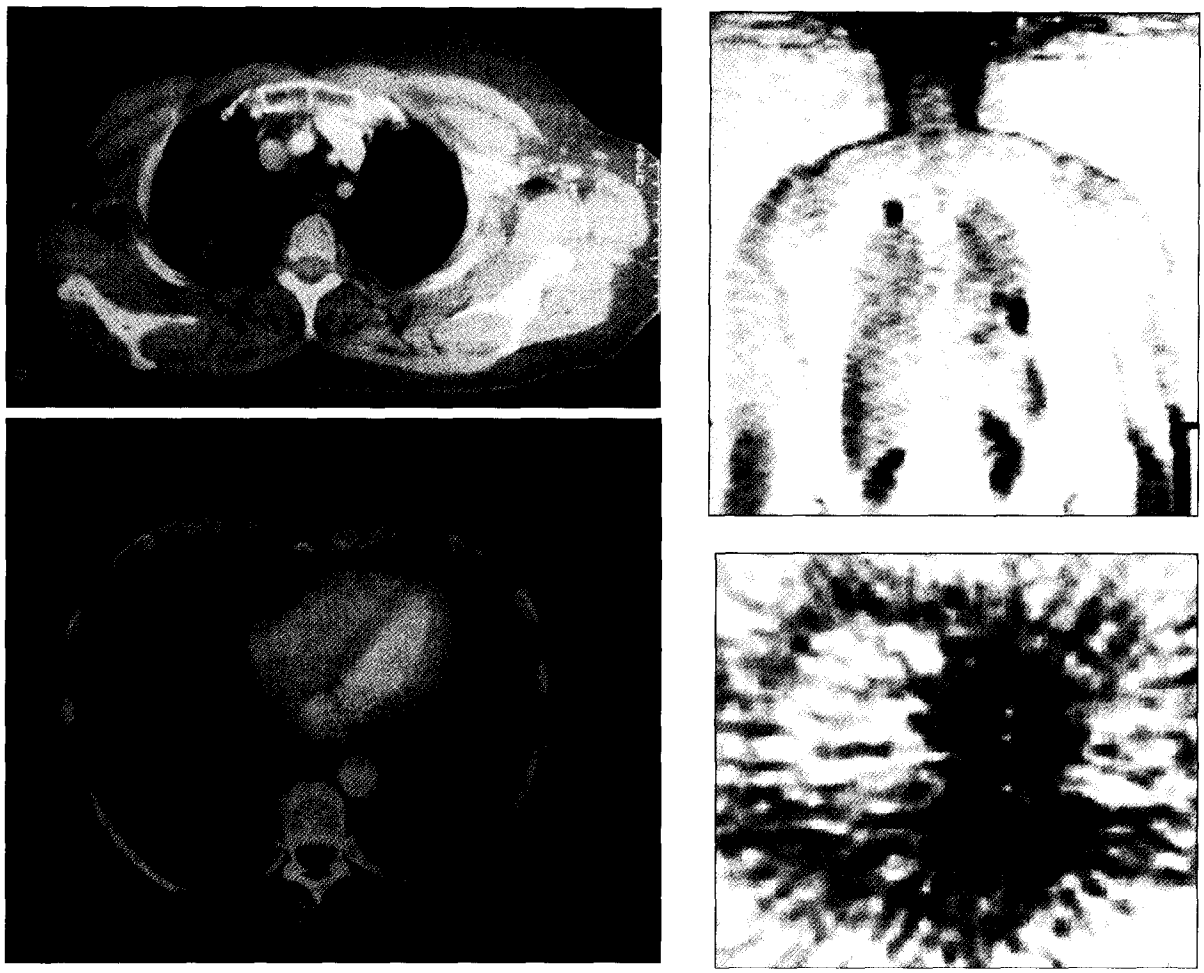

Fig. 1. Example of clinical staging in the presence of multiple pulmonary lesions (patient affected by Li-Fraumeni syndrome). (Left) spiral CT showed a lesion in right upper lobe and two lesions in the left lower lobe. (Right) PET confirmed the metabolic activity of the three lesions, without regional or distant metastases. Pathological examination after complete resection was indicative of three independent primary tumours. CT = computed tomography; PET = positron emission tomography.

specificity of PET were 95% and 83%, respectively. The use of PET for clinical staging resulted in a different stage from the one determined by standard methods in 62/102 (61%) patients: the stage was lowered in 20 and raised in 42. Whether PET scan has to be used systematically or in selected cases only (i.e. multiple lesions, Fig. 1) depends essentially on the availability and costs. In our experience, PET scan has proven very useful to assess the nature of additional lesions detected by CT scan [20] and avoid useless surgery in about 10% of cases. However, false-positive results are not infrequent due to chronic diseases such as granulomatous disorders or tuberculosis (TB), and pathological confirmation is often required.

Assessment of the functional status of the patient is a crucial component of the preoperative and pretreatment evaluation. Table 5 summarises the recommended tests to investigate cardio-pulmonary function before lung resection. With optimal use of these resources, it is possible to predict with great accuracy the immediate and long-term postoperative pulmonary function, as well as the overall periop-

Table 5
Preoperative functional evaluation

	Routine	High risk
Cardiac	ECG History and examination	ECHOcardiogram Exercise testing Myocardial scintigraphy Coronary angiogram
Pulmonary	Spirometry Blood gases	Lung perfusion scan Diffusing capacity (DLCO)

ECG = electrocardiogram.

erative risk of death, for a given resection volume. Perioperative mortality after lung cancer resection has constantly declined during the last two decades, and is now well below 3% in the major general thoracic surgical departments.

Surgical staging

In patients who are candidates for resection of NSCLC, the presence and extent of metastases in the mediastinal lymph nodes is one of the most important factors to predict the long-term prognosis and to select the appropriate management [21,22].

Whilst surgical treatment is generally indicated for clinical stage I and II, in patients with pathologically proven mediastinal lymph nodes metastases (mediastinoscopy positive, stage IIIA and IIIB) the prognosis is so poor (5% at 5 years) that primary resection is not justified in most instances [23].

Cervical mediastinoscopy and anterior mediastinotomy through the second intercostal space remain the gold standard for surgical assessment of the vast majority of suspicious nodes (>1 cm at CT or positive PET scan). Since the first description by Carlens, both procedures have proven to be very safe and reliable in nearly 40 years of clinical application. Upper and lower pre- and paratracheal, subcarinal, sub- and para-aortic nodes (stations R/L2–4, L5–6 and 7 according to the American Thoracic Society (ATS) map, Fig. 2) [24] can be reached in almost every case (Table 6). Distinct features such as extranodal spread, invasion of mediastinal fat, trachea or adjacent vessels, which may be of paramount relevance in the judgement of resectability after induction therapy,

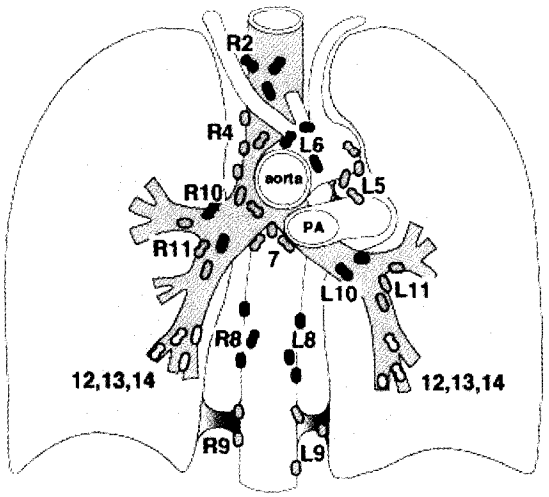

Fig. 2. New map of hilar and mediastinal lymph nodes (TNM-UICC 1997, Ref. [24]). PA = pulmonary artery.

Table 6
Surgical staging

Preoperative (pre-treatment)	In the case of suspicious N2–T4 at CT scan – Cervical mediastinoscopy – Anterior mediastinotomy (left upper lobe) – Routine biopsy of R(L)2–4 and 7 Cytology of pleural effusion
Intraoperative	Systematic mediastinal node dissection Mapping of nodal stations (ATS) Minimum sampling: R 2–4–7 (right), L 4–5–6–7 (left) Complete hilar dissection for segmentectomy Frozen section of relevant margins (bronchial / nodes) Pathological confirmation of unresectability

CT = computed tomography.

can only be evaluated by surgical exploration, certainly not by transbronchial needle aspiration biopsy. The combination of the two approaches is occasionally useful to assess difficult areas such as the subaortic fossa and the left tracheobronchial angle. Besides nodal staging, anterior mediastinotomy allows the assessment of primary tumour invasion of mediastinal vessels (T4), intrapericardial exploration, and direct pleuroscopy.

Accuracy rates of cervical mediastinoscopy range from 89% to 97% depending on the histological type and tumour location [25]. This relatively simple procedure allows thorough surgical exploration and pathological assessment of mediastinal lymph nodes, which yields the best clinical and pathological classification. It is essential that biopsies are taken from multiple lymph node levels, as well as controlateral nodes during the procedure to rule out multilevel and N3 disease, respectively.

In experienced hands, complications of cervical and para-sternal mediastinoscopy are rare (1–2%). Mediastinoscopy increases the cost of the evaluation of many patients. Nevertheless, when weighed against unnecessary thoracotomies the cost is insignificant.

In patients with normal mediastinal nodes at preoperative CT (cN0–1), the intraoperative surgical staging has the fundamental role of providing definitive pathological evidence of the status of parenchymal, hilar, mediastinal nodes, as well as of primary tumour and satellite nodules (Table 6). This part of the operation, that is crucial to decide the adequate volume of lung resection and provide accurate pathological staging, requires meticulous attention from the surgeon when performed through open thoracotomy. After radical lymph node dissection or systematic sampling, it is important that each nodal station is identified and labelled by the surgeon ac-

cording to the ATS map (Fig. 2) to facilitate the analysis of the pathologist and improve the accuracy of the final report [27].

Although in principle, the same level of accuracy may be achieved through video-assisted thoracic surgery (VATS), the anatomical problems (incomplete fissures, pleural adhesions, partial lung collapse) and excessive duration of surgery often lead to 'simpler' incomplete procedures with peripheral wedge resection and sampling of the few accessible lymph nodes. VATS has proven exceptionally useful in the assessment of patients with pleural effusion and negative percutaneous needle aspiration cytology. In those cases, thoracoscopic exploration of the pleural surface and guided biopsy of suspicious areas yields a much higher diagnostic accuracy.

TNM classification

The last edition of TNM [28] is reported in Tables 7 and 8 and illustrated in Fig. 3. Survivals for the different stages are illustrated in Table 9 and Fig. 4.

This revision of the TNM has provided only a limited contribution to the patients selection process by separating the T3 N0 tumours from the large group of stage IIIA and moving them to stage IIB. The other major change is the classification of satellite nodules as T4, if they are located in the same lobe of the primary tumour, or M1 otherwise. Unfortunately, such a proposal does not make any distinction between solitary and multiple nodules, thus posing a great problem of differential diagnosis with synchronous primaries. In terms of T classification, substantial problems remain unsolved such as the value of minimal pleural invasion, the

Table 8
Stage grouping: TNM subsets

Stage	TNM subset	
	A	B
0	Carcinoma in situ	
I	T1N0M0	T2N0M0
II	T1N1M0	T2N1M0
		T3N0M0
III	T3N1M0	T1–4N3M0
	T1–3N2M0	T4N0–2M0
IV	T1–4 N0–3 M1	

Table 7
TNM classification (WHO/AJC, 1997)

Primary tumour (T)	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour = 3 cm in greatest dimension, surrounded by lung or viscera pleura, without bronchoscopic signs of invasion more proximal than the lobar bronchus
T2	Tumour with any of the following features: – >3 cm in greatest dimension – involves main bronchus, = 2 cm distal to the carina – invades the visceral pleura – associated with atelectasis or obstructive pneumonitis that extends to the hilar region, but does not involve the entire lung
T3	Tumour of any size that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, mediastinal pleura, parietal pericardium; or tumour in the main bronchus < 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis that involves the entire lung
T4	Tumour of any size that directly invades any of the following: mediastinum, heart, great vessels, trachea, oesophagus, vertebral body, carina; or tumour with a malignant pleural or pericardial effusion, or with satellite tumour nodule(s) within the ipsilateral primary-tumour lobe of the lung
Regional lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes involved by direct extension of the primary tumour
N2	Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
Distant metastasis (M)	
Mx	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

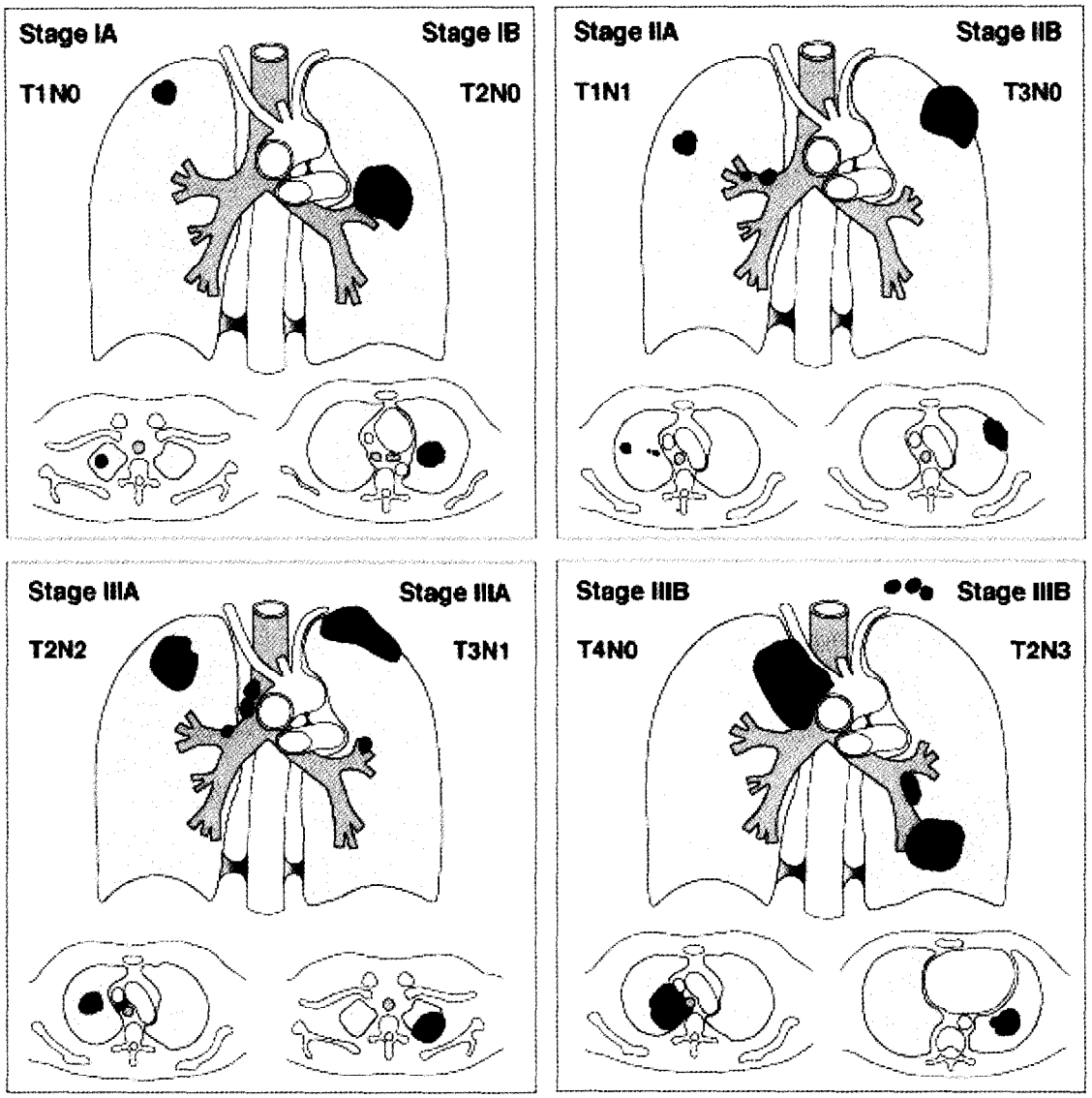

Fig. 3. Examples of different stage classifications, and relative CT scan image, according to the new classification system of TNM-UICC 1997 (Ref. [28]). UICC = Union International Centre Le Cancer; CT = computer tomographyion.

distinction between good T3 (mediastinal pleura, diaphragm, pericardium, main bronchus) and bad T3 (bone and soft tissues, Horner's, C7–8 involvement), and between technically resectable T4 (great vessels, atrium, trachea and carina, satellite nodules), marginally resectable (vertebral bodies, oesophagus) and unresectable T4 (heart ventricle, pleural effusion). Also, for the N classification, we still miss a uniform nodal map with unequivocal definition of N2 versus N3 at the pretracheal and subcarinal level, and accepted by American, European and Japanese surgeons. The present system is still grouping within the same stage (IIIA) patients with very different prognosis: bulky mediastinal disease, mediastinoscopy positive but resectable nodes, and clinically occult intraoperative N2. Moreover, the prognostic value of the number and/or proportion of positive hilar and mediastinal nodes, and of microscopic versus extranodal invasion, has never been properly assessed.

Minimal invasive approaches

The standard full postero-lateral thoracotomy with transection of major thoracic muscles is unnecessary in most cases of lung resection. Over 80% of procedures can be performed through muscle-sparing approaches with better functional and cosmetic results

A wide spectrum of limited, minimal invasive, thoracotomies can be applied to the majority of cases.

Table 9
Survival according to clinical and pathological TNM staging

	Survival (%)		
	1-year	3-year	5-year
Clinical staging			
IA	91	71	61
IB	72	46	38
IIA	79	38	34
IIB	59	33	24
IIIA	50	18	13
IIIB	34	7	5
IV	19	2	1
Pathological staging			
IA	94	80	67
IB	87	67	57
IIA	89	66	55
IIB	73	46	39
IIIA	64	32	23

Muscle-sparing techniques can be applied to posterolateral, axillary or anterolateral thoracotomies, with a skin incision of only 10–12 cm [29]. Latissimus dorsi is mobilised and retracted posteriorly, while the serratus muscle can be either freed and displaced anteriorly or split in the line of its fibres; thoracotomy is then performed through the 4th to 7th intercostal space (Fig. 5). Prospective randomised studies have demonstrated that muscle-sparing thoracotomies may be better than standard incisions in terms of early muscle strength, postoperative pain and pulmonary function, whereas the results at 6 months are similar [30,31]. In addition, anterior muscle-sparing approaches such as the trans-manubrial or hemiclamshell incisions may be useful in the management of apical tumours invading superior vena cava or subclavian vessels.

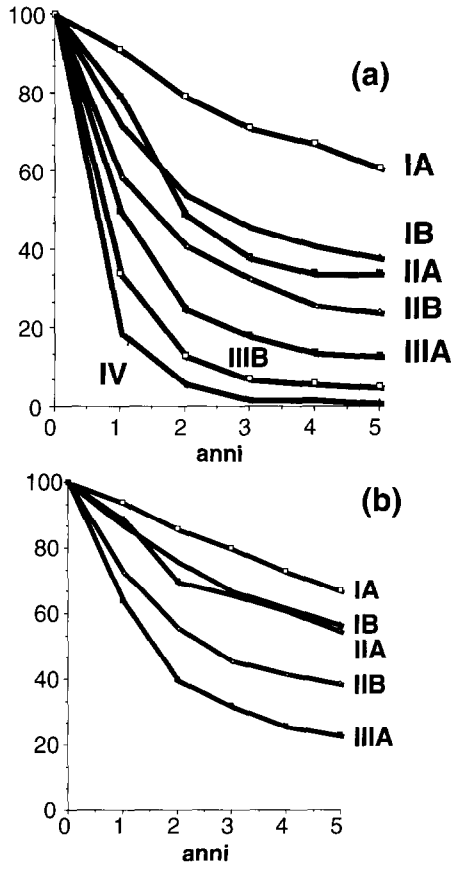

Fig. 4. Five-year survival according to the clinical (A) and pathological (B) TNM classification.

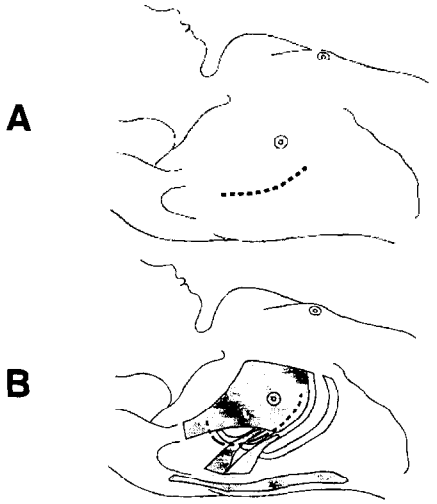

Fig. 5. Skin incision (A) for antero-lateral muscle-sparing thoracotomy, with preservation of latissimus dorsi, major pectoralis and serratus muscles, with access through the 4th or 5th intercostal space (B).

The new available technologies (fibreoptic and laser, microscopic high resolution cameras, mechanical staplers and suture devices, designed surgical instruments) have expanded the clinical use of endoscopic lung surgery, and a series of ideal indications for VATS have been defined with further experience (Table 10). Nonetheless, despite initial enthusiasm, the role of VATS in the curative treatment of NSCLC remains marginal and inappropriate use of thoracoscopic wedge resections has proven to be detrimental in patients with early stage disease and best expected prognosis [32].

VATS offers obvious advantages if compared with full posterolateral thoracotomy: small skin incisions, no intercostal spread, reduced bleeding, less postoperative pain and shorter hospital stay. However, the improved respiratory function and overall quality of life, often claimed on theoretical grounds, have never been convincingly demonstrated. Moreover, well recognised limitations such as extensive pleural

Table 10
Role of VATS in NSCLC

Staging	pleural metastases lower mediastinal adenopathies disseminated intrapulmonary disease.
Curative treatment	anatomical resection volumes (i.e. lobectomy) with clear surgical margins and adequate nodal dissection (segmental, lobar, hilar and mediastinal).
Palliative Treatment	pleural effusion: talc pleurodesis, pleuro-peritoneal shunt pericardial effusion: fenestration.
Safety issues	performed by experienced general thoracic surgeons specific training in video-assisted procedures proper surgical instruments.

NSCLS = non-small cell lung cancer.

adhesions, incomplete fissures (especially in severe emphysema), inadequate lung collapse, deeply located or hilar pulmonary lesions, are very frequent features in lung cancer patients. A popular misconcept is that VATS should be more suitable than thoracotomy for functionally compromised or high-risk patients. In reality, the surgical approach has very little if any impact on the operative risk, and patients with severe chronic obstructive pulmonary disease (COPD) may not tolerate the extent of lung collapse which is required for VATS. In the real world, VATS can only be applied to selected patients for 'easy' lobectomies, and in the majority of cases is likely to compromise the optimal procedure.

Limited resection for cT1N0

Retrospective historical series have provided inconclusive evidence that sublobar resections (segmentectomy, atypical wedge resection) may be as adequate as lobectomy for selected cases of early stage (T1N0) NSCLC [33]. In historical series, limited resection was usually offered to patients with poor respiratory function or prior lung resection, and based on the surgical assessment of the site and extent of disease at thoracotomy [34,35].

The question of the efficacy of limited resection for early lung cancer has been addressed in a randomised trial conducted by the Lung Cancer Study Group (LCSG) where 247 patients with NSCLC measuring 3 cm or less were randomised to lobectomy or limited resection (segmentectomy, wedge). To be eligible for the trial, patients had to fulfil very strict criteria at thoracotomy: peripheral lesion suitable for either procedure; frozen section analysis of segmental, lobar, hilar and mediastinal nodes to confirm the N0 status. The long-term results of this trial have recently been published and demonstrate a significant increase in the frequency of locoregional recurrence in the group treated by limited resection [36]. This high risk of relapse ultimately translated into a poorer long-term survival after 5–7 years. The trial was not designed to investigate the outcome of limited resection in specific clinical conditions such as compromised lung function or second primary lung cancer, but certainly does not support the elective use of wedge resection in early stage lung cancer. In addition, taking into account the problems of thoracoscopic assessment of segmental and lobar lymph nodes, one has to expect an even higher recurrence rate after atypical VATS resection for presumed T1N0 disease. A further problem observed in the early experience with VATS resection of peripheral NSCLC is the chest wall implant along the thoracoscopic port used to extract the specimen. Although recent standards would require protected extraction, with plastic bags or sleeves, and a proper intercostal incision, the number of patients presenting with local or chest wall recurrence is increasing.

Locoregional recurrence is a cause of greater concern in NSCLC than in other diseases such as breast cancer. In fact, it cannot be prevented by adjuvant external radiotherapy, it may occur very late (2–4 years after resection), it is very difficult to distinguish radiologically from fibrosis, and is almost impossible to salvage by completion lobectomy or pneumonectomy. In our experience, the vast majority of patients suffering from locoregional recurrence of NSCLC ultimately die of their disease, regardless of the salvage treatment.

The value of limited resection in very early lung cancer diagnosed by screening CT scan needs to be investigated in the future by controlled clinical trials.

Radical lobectomy can be performed by VATS in patients with favourable anatomical features: absence of pleural adhesions, complete fissure, adequate lung collapse, small peripheral tumour not involving the origin of the bronchus (sleeve lobectomy). Overall, such conditions occur in less than 5% of cases. Complete hilar and mediastinal node dissection, or even sampling, may prove difficult and time consuming. Multiple disposable instruments are required to perform vascular, parenchymal and bronchial sutures

with sufficient safety. At the end of the resection, a so-called 'utility thoracotomy' is invariably needed to extract the lobe, thus minimising the benefit of 'close chest' approach. In any case, VATS lobectomy must be performed by experienced thoracic surgeons to minimise the risk of major vascular bleeding, and guarantee a rapid conversion into open thoracotomy whenever required. Optimal resources and adequate training are essential, and the learning curve is critical.

Nodal dissection

Different policies can be applied by the surgeon in the management of hilar and mediastinal lymph nodes: remove them only if clearly metastatic, perform a systematic sampling of all nodal stations, perform a radical ipsilateral dissection, perform an extended dissection including bilateral nodes through median sternotomy or bilateral thoracotomy.

There is little doubt that radical nodal dissection results in a better pathological staging and a higher probability of complete resection at the local and regional level. In our experience, even for tumours below 2 cm of maximum diameter, occult N1 is present in 23% of patients and occult N2 disease in 14% [27]. The literature only offers three negative randomised trials [37], all underpowered due to very small number of patients, and one favourable report from the US intergroup trial [38]. Hopefully, the ongoing trial from the American College of Surgeons will provide a definitive contribution to clarify the ultimate survival benefit of nodal dissection in lung cancer.

New approaches to the Pancoast and T4 tumours

New modalities in the surgical approach to the tumours involving the superior sulcus and thoracic inlet, such as Pancoast, or with extensive invasion of great vessels or superior vena cava (SVC) and brachio-cephalic veins include the partial thoraco-sternotomy, also called hemiclamshell, and the transmanubrial approach (Fig. 6).

Transmanubrial osteomuscular sparing approach (TMA) [39] represents the evolution of the transclavicular technique initially proposed by Dartevelle [40]. This approach is particularly useful for treatment of the apical chest tumour to allow a safer subclavian artery control with a less invasive procedure for the patient [41]. TMA can be combined with the anterolateral muscle sparing thoracotomy to achieve extended resection of the cervico-thoracic

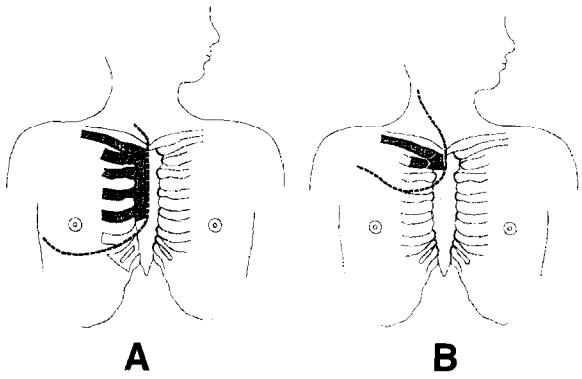

Fig. 6. New modalities of anterior cervico-thoracic approach: (A) partial thoraco-sternotomy or hemiclamshell; (B) trans-manubrial.

structures, as well as radical lobectomy and lymph nodes dissection [42], or with posterior Paulson's approach when rib disarticulation or vertebral resection is required to cope with chest wall invasion. If it is necessary to perform extended vascular resections, such as SVC replacement, TMA can be extended through a full median sternotomy or hemi-clamshell. TMA was conceived to avoid the deformities caused by the 'transclavicular' approach characterised by the sacrifice of the clavicle. In fact, by preserving the clavicle with its sternoclavicle articulation and the muscular insertions of the sternomastoid and major pectoral muscles, it prevents the anatomical and functional problems described by Jaklitsch and Rego [43]. However, with a larger clinical experience, TMA appears today to be quite different from other transcervical approaches allowing better exposure and easier extended resection for cancer.

TMA is characterised by an L-shape cervicotomy along the anterior part of the sternomastoid muscle and two fingers below the clavicle (Fig. 6). The clavicle is not divided as well as its muscular insertions (sternomastoid and major pectoral muscles). The chest wall under the clavicle is exposed having split the clavicular and sternal fibres of the major pectoral muscle. The manubrium is then sectioned with an L-shaped incision, and the first cartilage is resected after division of the internal mammary vessels. In order to lift the osteomuscular flap, the costoclavicular ligament has to be resected. This crucial manoeuvre allows the pincer formed by the first rib below and the clavicle above to be opened, thus exposing fully the subclavian vessels. This is technically demanding procedure since the ligament is very hard and the subclavian vein crosses the 1st rib just at the end of this structure. The section of the anterior scalenous muscle exposes the subclavian artery and its branches, which are then isolated and resected en bloc with the neoplasm, if necessary. The brachial

plexus is the last anatomical structure which it is possible to expose and resect (mainly C8–D1) when infiltrated by the tumour. When the apical portion of the tumour is completely freed from cervico-thoracic structures, the patient may be rotated 45° to perform the muscle-sparing antero-lateral thoracotomy or re-positioned for posterior thoracotomy, depending on the tumour extension.

Through the muscle-sparing thoracotomy, it is possible to perform any anatomical lung resection as well as radical mediastinal lymph nodes dissection (stations R2, 3, R4, 7, R8, R9, R10; L2, L4, 3, 5, 6, 10, 7, L8, L9), in addition to the cervical nodes dissection achieved by TMA. For lung tumours arising in the apex of the chest, it is not clear yet if the supraclavicular nodes have to be considered N1 or N3 stations. In our opinion, their involvement should not be judged as a formal contraindication to resection. On the other hand, cervical lymphadenectomy should be routinely performed in these tumours.

Transclavicular as well as TMA approaches have undoubtedly improve the surgical management of apical chest tumours, particularly for those requiring subclavian vessel dissection and resection [41]. Anatomical lung resection and radical lymph node dissection are the gold standard in lung cancer surgery, but require an additional thoracotomy or sternotomy. Moreover, the combined use of the muscle-sparing antero-lateral thoracotomy can improve the versatility of TMA allowing a correct en bloc resection of the tumour with the cervico-thoracic structures involved, with a safe hilar control during lung resection and a radical lymph node dissection, and a less invasive procedure for the patient.

Complex broncho-angioplastic procedures

Parenchymal saving procedures with bronchial and/or vascular reconstruction (Fig. 7) are commonly accepted as the treatment of choice for central lung cancers with suitable anatomy, even in patients with non-compromised function [44–47]. The safety of the technique, the adequacy of the operation and the better quality of life in comparison with pneumonectomy have been widely demonstrated by a number of retrospective studies [48–51].

The efficacy and wide application of multimodality therapy in locally advanced lung cancer has increased the number of patients that are candidate for surgery after chemotherapy. An increased risk of postoperative complications including acute respiratory distress syndrome (ARDS), bronchial fistula and empyema have been described for pneumonectomy following chemo- or chemoradiation therapy [52–54], but few data exist on the possible effects of induction treatment on bronchial suture and postoperative morbidity in patients submitted to sleeve procedures.

Macchiarini et al. [52] reported results of pneumonectomy with or without tracheal resection (9 and

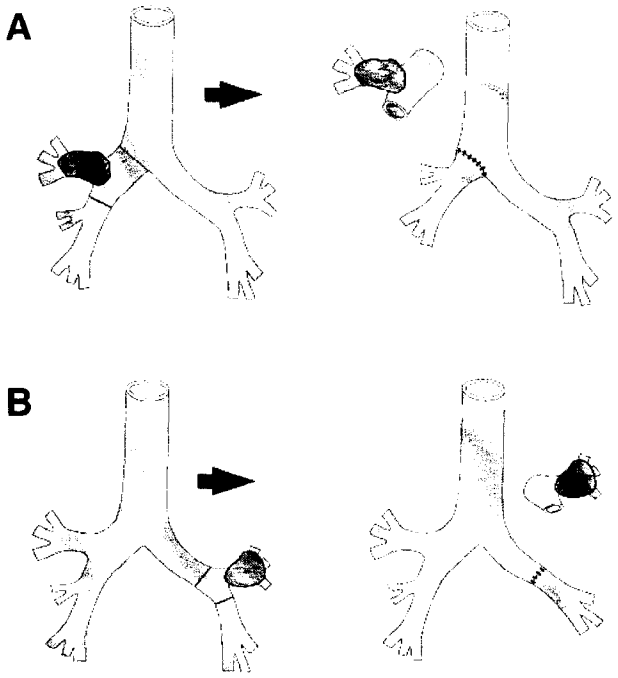

Fig. 7. Lobectomy with bronchial sleeve resection of the right (A) and left (B) upper lobe.

11 patients respectively) following induction chemo- or chemoradiation treatment for T4 disease: overall treatment-related mortality and the complication rate were 17% and 26% respectively. The complication rate was significantly higher among patients receiving chemoradiation therapy than among patients receiving only chemotherapy (42% vs 9%). Safety of the bronchoplastic procedure after chemotherapy was analysed by Rendina on 27 cases, who demonstrated that no added risk of complication was related to preoperative chemotherapy [55]. On the contrary, advantages in outcome were found after sleeve lobectomy or bilobectomy in comparison with standard pneumonectomy after induction treatment. Low morbidity rate, no mortality, no anastomotic dehiscence were associated to preoperative treatment in that series and 1 and 4 year survival rates were 78% and 39% (standard pneumonectomy 65% and 36%). Our experience confirms that sleeve resection after induction treatment is feasible, safe and does not interfere with postoperative mediastinal irradiation.

If necessary, sleeve resections can be combined with other angioplastic procedures such as pulmonary artery (or SVC) sleeve resection with direct end-to-end anastomosis or reconstruction with pericardial patch or prosthesis [56]. Taking into account the low morbidity rate and the adequate intraoperative radicality, broncho and/or angioplastic procedures should represent the treatment of choice after chemotherapy whenever technically feasible with pathological complete resection. Longer follow-up data are necessary to compare the efficacy of sleeve resection and pneumonectomy in terms of local control and survival in this series of patients [57].

Resection of the superior vena cava, although feasible in our experience [58], is rarely indicated in the treatment of NSCLC. Two recent papers showed not only the technical feasibility with low postoperative mortality, but also a noteworthy 5-year survival in patients with T4, N0–N1 disease [59,60]. However, more effective induction therapies have potentially expanded the benefit of locally extended resections [61].

We have recently reported that SVC resection can be combined with tracheal sleeve resection with no postoperative mortality, although we observed significant (50%) morbidity [62]. Combined tracheal sleeve and SVC resections are technical demanding procedures in which major difficulties are associated with uncertain oncological benefits. Our experience suggests anaesthesiological and technical feasibility of extended resections; the postoperative morbidity is high, but without fatal events. Even in our experience, the PTFE (polytetrafenylethylene) graft has remained patent as a long-term assessment [58]. Whilst curative potential of extended resection for locally advanced NSCLC has still to be defined, in selected T4N0 patients with SVC involvement, a radical resection, with or without bronchoplastic procedures, may achieve excellent local control with limited morbidity. On the contrary, in N2 disease, induction treatment is mandatory and the benefit of surgical resection versus radical radiotherapy has to be tested in prospective trials. In any case, pretreatment mediastinoscopy represents an essential staging procedure to select the optimal management in these highly selected patients.

Emphysema and lung cancer

It has been demonstrated by a recently published randomised trial that lung volume reduction improves pulmonary function in end-stage emphysema [63]. A similar volume reduction effect can be achieved by curative resection of cancers arising in the most compromised areas of the lung (usually the upper lobes). Korst, by analysing the experience of the Memorial Sloan Kettering, has demonstrated that patients with a very low preoperative forced expiratory volume 1 (FEV1) and FEV1 to forced vital capacity ratio are less likely to lose ventilatory function after lobectomy and may actually improve it [64].

Based on such experience, the indications for surgery in emphysematous patients have been gradually extended. We routinely operate upon patients suffering from lung cancer (even bilateral) and severe emphysema, with good local control of cancer and significant functional rescue.

Future research prospects are aimed at combining surgery with stereotactic or intraoperative radiotherapy in properly selected patients. In fact, recent developments in radiotherapy opens new possibilities for the conservative management of early stage lung cancer in patients with very compromised cardiopulmonary function or severe comorbidity. Corporeal stereotactic radiation, using single or multiple fractions, may be able to eradicate small (1–2 cm), peripheral pulmonary lesions with limited damage to the surrounding parenchyma and adjacent organs. On the other hand, superficial endobronchial lesions may be successfully treated by endoluminal brachytherapy. Along the same lines, multiple synchronous or metachronous primary lung cancers can be approached by a combination of surgery and radiotherapy, depending on the size and location of tumours. In this highly selected population of patients bearing

multiple pulmonary lesions, a PET scan represents an extremely valuable instrument to improve clinical staging and rule out nodal metastases. It is likely that in the near future, as a consequence of further technological improvements, a significant proportion of lung cancers detected in compromised patients will be offered local radiotherapy as a primary treatment, keeping surgical resection as a salvage therapy for those cases who failed to obtain permanent local control.

Induction chemotherapy

Induction (neo-adjuvant) chemotherapy emerged as an option for patients with N2 disease after it became clear that only a minority of these patients could benefit from surgical resection alone and that preoperative radiotherapy had no effect on survival [23]. As the ability to perform a complete surgical resection, for locally advanced tumours, seems to play an important role in the management of this disease, a treatment modality that could reduce the tumour burden preoperatively might be useful to achieve a larger number of complete resections. Another potential benefit of induction chemotherapy is the fact that patients tend to be more compliant and less immuno-suppressed prior to surgery than they are in the post-operative period, and the pathological effect of chemotherapy on the tumours can be assessed more accurately, since resection occurs following chemotherapy. Furthermore, induction chemotherapy could eradicate micrometastatic disease, already present at the time of surgery, and thereby prolong survival.

Induction chemotherapy followed by surgical resection and radiotherapy has been shown to improve survival in small randomised trials, as well as in larger phase II studies [65], when results are compared with historical controls.

Three phase III trials tested induction chemotherapy followed by surgery versus primary surgical resection in patients with clinical stage IIIA disease [66–68]. Although different chemotherapy protocols were used and the number of patients was small, the survival rates reported were significantly higher than in the control arms. In these studies, the rate of complete resection was not different in the treatment arms compared with the control arms.

However, these trials have been criticised due to patient selection, inaccurate staging and very short survival in the non-chemotherapy arm. In fact, only a few selected cases entered these trials out of several hundreds of patients treated within the same period, cN2 disease was not pathologically proven in all cases, and patients who underwent primary surgery for cT3N0 disease showed a dismal prognosis. Moreover, the chemotherapy and radiotherapy protocols varied widely from one trial to the next.

In the meantime, chemotherapy with radiation has been evaluated in phase II and III trials as a definitive procedure for local control instead of surgical resection. Overall, there seems to be a modest survival benefit for chemotherapy added to primary radiation therapy, both combined and sequential when compared with radiotherapy alone. The overall 5-year survival figures are similar to those obtained in trials of locally advanced resectable disease incorporating surgical resection as part of the multimodality therapy. Results of on-going randomised trials are needed to compare these two approaches of primary control, as well as to define the role of standard adjuvant chemotherapy in patients with stage IIIA NSCLC.

In less advanced lung cancer, or intrapulmonary disease (T2N0 or T1–2N1 at CT scan), surgery alone can achieve a 40–50% 5-year survival. Still, nearly half of the patients die because of recurrent disease and the prognosis is poor enough to justify adjuvant therapies. Recent meta-analyses of randomised trials have shown no benefit for postoperative radiotherapy and a limited benefit for cisplatin-based postoperative chemotherapy. Large on-going trials in Europe will hopefully clarify the real benefit of adjuvant chemotherapy in operable NSCLC. However, it is invariably true in every experience that chemotherapy, if applied after lung resection, can only be tolerated at full doses by a fraction of the randomised patients.

Moving chemotherapy upfront has several potential advantages in operable disease: better compliance, earlier treatment of occult residual disease, tumour shrinkage and downstaging leading to a smaller resection volume, as well as true pathological assessment of response. Other, more theoretical, benefits include: prevention of viable tumour seeding at the time of surgery and of tumour promotion induced by immunosuppression or growth factor release after major surgery.

Given this rationale and scientific background, two multicentric randomised trials have been launched to evaluate two different schemes of preoperative chemotherapy in patients with operable NSCLC (stage IB-II, and T3N1). The two twin studies will be conducted in parallel with the same study protocol, except the drug combination, and patients will be randomised to 3 cycles of chemotherapy followed by surgery versus immediate surgery. The first trial, named BLOT or NOT, has been promoted by the US intergroup and supported by the NCI in the United States, will use carboplatin and paclitaxel

for three cycles. The other Italian-based multicentric trial, named CHEST (Chemotherapy for Early Stage Tumours), will use cisplatin and gemcitabine for three cycles and is expected to randomise 650 patients within 3 years.

Multiple lung cancers

Multiple primary tumours may arise in the lung as a consequence of chronic widespread exposure of its epithelium to a multiplicity of carcinogens contained in tobacco smoking, sometimes in association with other environmental risk factors. This process is well known in upper aerodigestive cancers as a 'field cancerization' effect. In patients cured for a cancer of the lung, cumulative frequency of second primary tumours in all sites is 10–25%, with a relatively constant incidence of 2 to 3% per year. Most of these second tumours occur in the lung (8–20% overall) and are metachronous, but in 10 to 15% of cases they are synchronous. In a cohort of 659 Stage I lung cancers, with a median observation time of 64 months (9 years in survivors), we detected a total of 213 (32%) independent primary cancers in 170 (26%) patients; of the 97 lung cancers, 15 were detected at the same time as the index tumour. These figures are remarkably similar to those reported by Martini, based on 598 patients treated at Memorial Hospital.

The differential diagnosis between metastatic disease and second primary lung cancer may be extremely difficult in some cases. Traditional criteria based on the anatomical site (distance from main cancer, different lobe) or histological type have proven ineffective. In our experience, 60% of new primaries showed the same histological type as the prior lung cancer. A number of studies have provided evidence that molecular markers are superior to clinical or pathological assessment in the differential diagnosis of multiple primary tumours, but their implementation in clinical practice is still difficult.

With a constant improvement of diagnostic tools, such as spiral CT, detection of additional nodules in patients with lung cancer is becoming more and more frequent. Clinical significance of such lesions depends on the number, size and other morphological features, as well as on the extent of the primary tumour. In patients presenting with more than two pulmonary nodules, the final diagnosis is often metastatic disease. However, when only two lesions are visible at spiral CT, synchronous primaries or concurrent benign disease (hamartoma, granuloma, TB) are more likely. The recent introduction of the PET scan has provided an extremely useful tool for the clinical staging of patients with multiple nodules.

Patients presenting with multiple primary tumours should never labelled as metastatic disease, because their prognosis may be favourable if each individual lesion can be approached with curative intent. In the cohort of patients already mentioned, 50% of multiple lung cancers achieved a complete resection and 5-year survival was not significantly different from rates for patients with solitary tumours. These figures were very similar to those reported by other cancer centres. Modern developments of early detection, conservative pulmonary surgery, volume reduction physiology, and stereotactic lung radiation represent new effective modalities to approach the problem of multiple lung cancers with curative intent.

Chemoprevention of upper aerodigestive tract cancer has proven feasible in the experimental setting [69], but clinical evidence of a beneficial effect in humans is still limited and controversial. Despite initial promising results [70], large randomised trials have shown no activity or detrimental results [71]. In order to justify future clinical experiments, two elements are essential: selection of individuals with a much higher risk of cancer and discovery of more effective drugs. Topical application of chemopreventive agents is a logical way to circumvent their systemic toxicity and to increase pharmacological levels in the target tissues [72]. This is particularly sound for retinoids with a view to their well established capacity to induce regression of skin cancer and other dermatological diseases by topical application. Pilot studies on inhalation of aerosolised retinoids are on-going in the United States and Europe using all-*trans* retinoic acid (RA) and 13*cis*RA via an aerosol [73].

References

1 Murray CJL, Lopez AD (Eds.). The Global Burden of Disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. 1996, Harvard University Press, Cambridge.
2 Nesbitt JC, Putnam JB, Walsh GL, Roth JA, Mountain CF. Survival in early-stage lung cancer. Ann Thorac Surg 1995, 60: 466–472.
3 Shah R, Sabanathan S, Richardson J, Means AJ, Goulden C. Results of surgical treatment of stage I and II lung cancer. J Cardiovasc Surg 1996, 37: 169–172.
4 Sobue T, Suzuki R, Matsuda M, Kuroishi T, Ikedi S, Naruke T. Survival for clinical stage I lung cancer not surgically treated. Cancer 1992, 69: 685–692.
5 Patz EF, Rossi S, Harpole DH, Herndon JE, Goodman PC. Correlation of tumour size and survival in patients with stage Ia non-small cell lung cancer. Chest 2000, 117: 1568–1571.
6 Melamed MR, Flehinger BJ, Zaman MB, Heelan RT, Parchick WA, Martini N. Screening for lung cancer: results of the

Memorial Sloan-Kettering study in New York. Chest 1984, 86: 44–53.
7 Tockman MS. Survival and mortality from lung cancer in a screened population: the John Hopkins Study. Chest 1986, 89: 324–325S.
8 Fontana RS, Sanderson DR, Woolner LB et al. Lung cancer screening: the Mayo program. J Occup Med 1986, 28: 746–750.
9 Kubik A, Parkin DM, Khlat M, Erban J, Polak J, Adamee M. Lack of benefit from semi-annual screening for cancer of the lung: follow-up report of a randomised controlled trial on a population of high risk males in Czechozlovakia. Int J Cancer 1990, 45: 26–33.
10 Kaneko M, Eguchi K, Ohmatsu H, Kakinuma R, Naruke T, Suemasu K, Moriyama N. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. Radiology 1996, 201: 798–802.
11 Sone S, Takashima S, Li F, Yang Z, Honda T, Maruyama Y, Hasegawa M, Yamanda T, Kubo K, Hanamura K, Asakura K. Mass screening for lung cancer with mobile spiral computed tomography scanner. Lancet 1998, 351: 1242–1245.
12 Henschke CI, McCauley DI, Yankelevitz DF, Naidich DP, McGuinness G, Miettinen OS, Libby DM, Pasmantier MW, Koizumi J, Altorki NK, Smith JP. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 1999, 354: 99–105.
13 Mulshine JL, De Luca LM, Dedrick RL, Tockman MS, Webster R, Placke ME. Considerations in developing successful population-based molecular screening and prevention of lung cancer. International Conference on Prevention and Early Diagnosis of Lung Cancer, Varese, Italy, 1998, pp. 121–125.
14 Sozzi G, Musso K, Ratcliffe C, Goldstraw P, Pierotti MA, Pastorino U. Detection of microsatellite alterations in plasma DNA of non-small cell lung cancer patients: a prospect for early diagnosis. Clin Caner Res 1999, 5: 2689–2692.
15 Anonimous. The World Health Organization. Histological typing of lung tumours. Am J Clin Pathol 1982, 77: 123–136.
16 Colby TV, Koss MN, Travis WD. Tumours of the lower respiratory tract. In: Anonimous Atlas of tumour pathology, Washington, Armed Forces Institute of Pathology, 1994.
17 Lowe VJ, Naunheim KS. Positron emission tomography in lung cancer. Ann Thorac Surg 1998, 65: 1821–1829.
18 Kernstine KH, Stanford W, Mullan FB et al. PET, CT, and MRI with Combidex for mediastinal staging in NSCLC. Ann Thorac Surg 1999, 68: 1022–1028.
19 Pieterman RM, van Putten JW, Meuzelaar J et aL. Preoperative staging of NSCLC with positron-emission tomography. N Engl J Med 2000, 343: 4.
20 Kutlu CA, Pastorino U, Maisey M, Goldstraw P. Selective use of PET scan in the preoperative staging of NSCLC Lung Cancer 1998, 21: 177–184.
21 Naruke T, Goya T, Tsuchiya R et al. The importance of surgery to non-small cell carcinoma of the lung with mediastinal lymph node metastasis. Ann Thorac Surg 1988, 46: 603.
22 Goldstraw P, Mannam GC, Kaplan DK et al. Surgical management of non-small cell lung cancer with ipsilateral mediastinal node metastasis (N2 disease). J Thorac Cardiovasc Surg 1994, 107: 19.
23 Pearson FG, Delarue NC, Ilves R et al. Significance of positive superior mediastinal nodes identified at mediastinoscopy in patients with resectable cancer of the lung. J Thorac Cardiovasc Surg 1982, 83: 1.
24 Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. Chest 1997, 111: 1718–1723.
25 Patterson GA, Ginsberg RJ, Poon PY et al. A prospective evaluation of magnetic resonance imaging, computed tomography, and mediastinoscopy in the preoperative assesement of mediastinal node status in bronchogenic carcinoma. J Thorac Cardiovasc Surg 1987, 94: 679–684.
26 Dilemmans B, Deneffe G, Verschakelen J et al. Value of computed tomography and mediastinoscopy in preoperative evaluation of mediastinal nodes in NSCLC. Eur J Cardiothoracic Surg 1994, 8: 37–42.
27 Graham AN, Chan KJ, Pastorino U et Al. Systematic nodal dissection in the intrathoracic staging of patients with NSCLC. J Thorac Cardiovasc Surg 1999, 117: 246–251.
28 Mountain CF. Revision of the international system for staging lung cancer. Chest 1997, 111: 1710–1717.
29 Pastorino U. Valente M, Muscolino G, Andreani S, Ravasi G. Muscle-sparing anterolateral thoracotomy for pulmonary or mediastinal resections. In: G. Motta (Ed.), Lung Cancer. Frontiers in Science and Treatment. Grafica LP, Genoa, 1994, pp. 337–341.
30 Lemmer JH Jr, Gomez MN, Symreng T, Ross AF, Rossi NP. Limited lateral thoracotomy. Improved postoperative pulmonary function. Arch Surg 1990, 125: 873–877.
31 Hazelrigg SR, Landreneau RJ, Boley TM, Priesmeyer M, Schmaltz RA, Nawarawong W, Johnson JA, Walls JT, Curtis JJ. The effect of muscle-sparing versus standard posterolateral thoracotomy on pulmonary function, muscle strength, and postoperative pain. J Thorac Cardiovasc Surg 1991, 101: 394–400.
32 Allen MS, Pairolero PC. Inadequacy, mortality and thoracoscopy. Ann Thorac Surg 1995, 59: 6.
33 Ginsberg RJ. Limited resection in the treatment of stage I non-small cell lung cancer — an overview. Lung Cancer 1988, 4: 40.
34 Shields TW, Robinette CD. Long-term survivors after resection of bronchial carcinoma. Surg Gyn Obst 1973, 136: 759–768.
35 Jensik RJ. The role of segmental resection in lung cancer. Chest 1986, 89: 335.
36 Lung Cancer Study Group. Randomized trial of lobectomy versus limited resection for T1N0 non-small cell lung cancer. Ann Thorac Surg 1995, 60: 615–623.
37 Izbicki JR, Passlick B, Pantel K, Pichlmeier U, Hosch SB, Karg O, Thetter O. Effectiveness of radical systematic mediastinal lymphadenectomy in patients with resectable non-small cell lung cancer: results of a prospective randomized trial. Annals of Surgery. 1998, 227: 138–144.
38 Keller SM, Adak S, Wagner H, Johnson DH. Mediastinal lymph node dissection improves survival in patients with stages II and IIIa non-small cell lung cancer. Eastern Cooperative Oncology Group. Ann Thorac Surg 2000, 70: 358–365; discussion 365–366.
39 Grunenwald D, Spaggiari L, Girard P, Baldeyrou P. Transmanubrial approach to the thoracic inlet. J Thorac Cardiovasc Surg 1997, 113: 958–959.
40 Dartevelle P, Chapelier AR, Macchiarini P. Anterior transcervical-thoracic approach for radical resection of lung tumours invading the thoracic inlet. J Thorac Cardiovasc Surg 1993, 105: 1025–1034.
41 Spaggiari L, Pastorino U. Subclavian artery involvement by apical chest tumours: a specific indication for the transmanubrial approach. J Thorac Cardiovasc Surg 1999, 117: 627 (letter).
42 Spaggiari L, Pastorino U. Transmanubrial approach with antero-lateral thoracotomy for apical chest tumours. Ann Thorac Surg 1999, 68: 590–593.

43 Jaklitsch MT, Rego A. Endorsement for sparing the clavicle in the transcervical approach to the thoracic inlet. J Thorac Cardiovasc Surg 1997, 113: 959–960.
44 Paulson DL, Urschel HC, Judson McNamara J, Shaw RR. Bronchoplastic procedures for bronchogenic carcinoma. J Thorac Cardiovasc Surg. 1970, 59: 38–48.
45 Wiesel R, Cooper JD, Delarue C, Theman TE, Todd TRJ, Griffith Pearson F. Sleeve lobectomy for carcinoma of the lung. J Thorac Cardiovasc Surg 1979, 78: 839–849.
46 Deslauriers J, Gaulin P, Beaulieu M, Piraux M, Bernier R, Cormier Y. Long-term clinical and functional results of sleeve lobectomy for primary lung cancer. J Thorac Cardiovasc Surg 1986, 92: 871–879.
47 Gaissert HA, Mathisen DJ, Moncure AC, Hilgenberg AD, Grillo HC, Wain JC. Survival and function after sleeve lobectomy for lung cancer. J Thorac Cardiovasc Surg 1996, 111: 948–953.
48 Kutlu CA, Goldstraw P. Tracheobronchial sleeve resection with the use of a continuous anastomosis: results of one hundred consecutive cases. J Thorac Cardiovasc Surg 1999, 117: 1112–1117.
49 Icard I, Regnard JF, Guibert L, Magdaleinat B, Jauffret B, Levasseur P. Survival and prognostic factors in patients undergoing parenchymal saving bronchoplastic operation for prymary lung cancer: a series of 110 consecutive cases. Eur J Cardio-Thorac Surg 1999, 15: 426–432.
50 Read RC, Ziomek S, Ranval T, Eidt JF, Gocio JC, Schaefer RF. Pulmonary artery sleeve resection for abutting left upper lobe lesions. Ann Thorac Surg 1993, 55: 850–854.
51 Rendina EA, Venuta F, De Giacomo T, Coloni GF. Sleeve resection and prosthetic reconstruction of the pulmonary artery for lung cancer. Ann Thor Surg 1999, 68: 995–1000.
52 Macchiarini P, Chapelier AR, Monnet I, Vannetzel JM, Rebischung JL, Cerrina J, Parquin F, Ladurie FLR, Lenot B, Dartevelle P. Extended operations after induction therapy for stage IIIb non small cell lung cancer. Ann Thorac Surg 1994, 57: 966–973.
53 Rush VW, Albain KS, Crowley JJ, Rice TW, Lonchyna V, Benfield JR. Surgical resection of stage IIIA and IIIB non small cell lung cancer after concurrent induction chemotherapy. A Southwest Oncology Group Trial. J. Thorac and Cardiovasc Surg 1993, 105: 97–106.
54 Fowler WC, Langer CJ, Curran WJ, Keller MJ. Postoperative complications after combined neoadjuvant treatment of lung cancer. Ann Thorac Surg 1993, 55: 986–989.
55 Rendina EA, Venuta F, De Giacomo T, Flaishman I, Fazi P, Ricci C. Safety and efficacy of bronchovascular reconstruction after induction chemotherapy for lung cancer. J Thorac Cardiovasc Surg 1997, 114: 831–837.
56 Solli PG, Spaggiari L, Grasso F, Pastorino U. Double Prosthetic Replacement Of Pulmonary Artery And Superior Vena Cava And Sleeve Lobectomy For Lung Cancer. Eur J Cardio-Thorac Surg 2001, in press.
57 Van Schill P, Vankeirsbilck, Brutel de la Riviere A, van des Bosch JM. Long term survival after bronchial sleeve resection in relation to nodal involvement. Eur J Cardio-Thorac Surg 2000, 17: 196–197.
58 Dartevelle PG, Chapelier A, Pastorino U et al. Long-term follow-up after prosthetic replacement of the superior vena cava combined with the resection of mediastinal-pulmonary malignant tumours. J Thorac Cardiovasc Surg 1991, 102: 259–265.
59 Thomas P, Magnan PE, Moulin G, Giudicelli R, Fuentes P. Extended operation for lung cancer invading the superior vena cava. Eur J Cardio-thorac Surg 1994, 8: 177–182.
60 Spaggiari L, Regnard JF, Magdeleinat P, Jauffret B, Puyo P, Levasseur P. Extended resections for bronchogenic carcinoma invading the superior vena cava system. Ann Thorac Surg 2000, in press.
61 Dartevelle PG. Extended operations for the treatment of lung cancer. Ann Thorac Surg 1997, 63: 12–9.
62 Spaggiari L, Pastorino U. Combined tracheal sleeve and superior vena cava resections for non-small cell lung cancer. Ann Thorac Surg 2000, 70: 1172–1175.
63 Geddes D, Davies M, Koyama H, Hansell D, Pastorino U, Pepper J, Agent P, Cullinan P, MacNeill SJ, Goldstraw P. Effect of lung-volume-reduction surgery in patients with severe emphysema. N Engl J Med 2000, 343: 239–245.
64 Korst RJ, Ginsberg RJ, Ailawadi M, Bains MS, Downey RJ Jr, Rusch VW, Stover D, Heitmiller RF, Altorki NK, Condon JK, Cerfolio RJ, Kohman LJ, Ginsberg RJ. Lobectomy improves ventilatory function in selected patients with severe COPD. Ann Thorac Surg 1998, 66: 898–902.
65 Martini N, Kris MM, Flehinger BJ et al. Preoperative chemotherapy of stage IIIA (N2) NSCLC: The Memorial Sloan-Kettering experience with 136 patients. Ann Thorac Surg 1993, 55: 1365–1374.
66 Pass HI,PogrebniakHW, Steiberg SM et al. Randomized trial of neoadjuvant therapy for lung cancer: interim analysis. Ann Thorac Surg 1992, 53: 992–998.
67 Rosell R, Gomez-Condima J, Camps C et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with NSCLC. N Engl J Med 1994, 330: 153–158.
68 Roth JA, Atkinson EN, Fossella F et al. Long term follow-up of patiens enroled in a randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA NSCLC. Lung Cancer 1998, 21: 1–6.
69 Lotan R. Effects of vitamin A and its analogs (retinoids) on normal and neoplastic cells. Biochim Biophys Acta 1980, 605: 33–91.
70 Pastorino U, Infante M, Maioli M, Chiesa G, Buyse M, Firket P, Rosmentz N, Clerici M, Soresi E, Valente M, Belloni PA, Ravasi G. Adjuvant treatment of stage I lung cancer with high-dose vitamin A. J Clin Oncol 1993, 11: 1216–1222.
71 van Zandwijk N, Dalesio O, Pastorino U, de Vries N, van Tinteren H, for the European Organization for Research and Treatment of Cancer Head and Neck and Lung Cancer Cooperative Groups. EUROSCAN, a randomized trial of vitamin A and N-acetylcysteine in patients with head and neck cancer or lung cancer. J Natl Cancer Inst 2000, 92: 977–986.
72 Raleigh SM, Verschoyle RD, Bowskill C, Pastorino U, Staniforth JN, Steele F, Dinsdale D, Carthew P, Lim CK, Silvester J, Gescher A. Pulmonary availability of isotretinoin in rats after inhalation of a powder aerosol. Br J Cancer 2000, 83: 935–940.
73 Brooks AD, Benedetti F, Tong WP, Miller VA, Burt M, Kris MG, Warrel RP. Chemoprevention of respiratory tract cancers. Proc Am Ass Cancer Res (AACR) 1997, 38: 574, 86.