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Surgical results and survival of older patients with unsuspected N_2 (stage IIIA) non-small cell lung cancer

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SUMMARY: **Surgical results and survival of older patients with unsuspected N2 (stage IIIA) non-small cell lung cancer.**

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Purposes. *The optimal treatment of N2 non-small cell lung cancer (NSCLC) in older patients is still debate and represent an important treatment and ethical problem.*

Patients and methods. *Between January 2000 to December 2010, 273 older patients underwent lung resection for (NSCLC).*

Results. *The overall-operative mortality was 9.5%. Risk factors for in-hospital mortality were pneumonectomy and poli-vasculopathy. One, 3 and 5-year survival were 73%, 23% and 16% respectively.*

Conclusions. *In potentially operable older patients with NSCLC we need to make every effort to exclude N2 involvement because very poor long-term survival. Pneumonectomy in older patients gains prohibitive in-hospital mortality.*

KEY WORDS: Lung cancer - Advanced stage - Older patients - Extended resection.

Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer death in the Western Countries with a highest incidence in the seventh decade of life (1). Because of the continuum aging of the population in the industrialized countries, more frequently neoplastic older patients with multi-morbidities are referred to thoracic surgery departments. The role of surgery alone or in combination with chemo-radiotherapy in older patients with advanced stage NSCLC is still under debate (1-3). A careful selection of patients is mandatory to reduce operative mortality and morbidity, and to guarantee a good quality of life and a potential benefit in term of life expectancy. Despite all this efforts it as been estimated that one-fourth of patients with negative preoperative mediastinal nodal staging have occult N_2 lymph nodes involvement (2).

We report our experience in case of IIIA occult N_2 disease in older patients with NSCLC.

Patients and methods

The data and variables were collected retrospectively from lung cancer data base of two thoracic surgery units, selecting patients aged >75 years who underwent intended curative lung resection for NSCLC between January 2000 to December 2010. We identify 273 older patients (age >75years) representing the 6.4% of 4,286 lung resection performed during the study period. In order to understand the surgical outcome and follow-up prognosis of older patients with advanced pathological stage NSCLC, we extrapolate from this population 42 (15.4%) patients with pIIIA cancer stage according with the 2009 revised lung cancer staging system (4). Thirty-three (78.6%) of these patients were operated before the routinely application of PET/CT-scan in preoperative work-up of our hospitals. Four patients had stage pIIIA T_4-N_1 (9.5%) and one patient had stage pIIIA T_3-N_1 (2.4%). All the other patients were classified stage pIIIA due to pN_2 involvement (88%, 37 patients).

Before the introduction of PET the evaluation of mediastinal nodes were done with CT-scan, and only patients with lymph nodes greater then 10mm were considered at risk for metastasis. In this case mediastinoscopy was performed. In case of confirmation of clinical (c)-N_2 disease surgery will be denied in these patients. After the advent of PET technology, if the CT scan showed enlarged lymph nodes (>10mm) PET/CT was performed. In case of PET-positive lymph nodes, mediastinoscopy and/or endoscopic esophageal ultrasound (EUS) and/or endoscopic bronchial ultrasound (EBUS) were performed. Again, in case of confirmation of cN_2 disease the patients were

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not scheduled for surgery. Indeed, this 42 patients represent a particular sub-groups in which the preoperative work-up was negative for the suspicion of cN_2 disease because of dimension lymph nodes <10mm at the CT-scan or because lymph nodes negative at PET. According to the 2007 American College of Chest Physicians (ACCP) practice guidelines (2) for the treatment of NSCLC stage IIIA these patients could be sub-classified as $pIIIA_{1-2}$, defined as incidental nodal metastasis found on final pathology examination of the resection specimen or a single nodal metastases recognized intraoperatively, from the original definition reported by Ruckdeschel et al (5).

The mean age of the study population was 77.8±3.1 years (range 75-87 years). There were 39 males (93%) and 3 females (7%). Most of them had history of cigarette smoking (27 patients, 64.3%), 11 patients were still smokers (26.2%). The mean forced expiratory volume in 1 second (FEV_1) was 1,64L (range 0.71-2.73L), 9 patients had a low respiratory reserve (FEV_1<70%) (21.4%). The other associated comorbidities were reported in Table 1. Twenty-seven patients (64.3%) had more than one comorbidities. Preoperative performance status was 1.9±0.8 according to the Zubrod-Score (6). One patient had a previous right upper lobectomy for adenocarcinoma staged at the time of first resection as IB. Two patients with high performance status and a T4 adenocarcinoma received induction chemo/radiotherapy.

Nine-teen patients (45.2%) were clinically staged as cIB, 13 cIIA (31%), 5 cIIB (11.9%), 5 cIIIA (N_1)(11.9%).

Statistics were performed using SPSS (Statistical Package for Social Science) version 11.0 for Windows (SPSS, Inc, Chicago, Ill, USA). All data were collected retrospectively from institutional data bases. Continuous variable were given as mean±SD, categorical variables were given as a percentages. In-hospital risk factors for mortality and morbidity were analysed using a binary logistic-regression-model. The Cox-multivariate-regression was used to identify independent prognostic factors for long-term mortality using a stepwise model. A p-value less than 0.05 was considered to be statistically significant. Survival analysis was conducted according to the Kaplan-Meier method, curves were compared by the long-rank test.

TABLE 1 - PATIENTS COMORBIDITIES.

Comorbidity	Patients, n
Systemic hypertension	27(64.3%)
COPD	19(45.2%)
Poli-vasculopathy	8(19%)
Chronic ischemic cardiomyopathy	9(21.4%)
Previous CVE	3(7.1%)
Chronic renal failure (creatinine>2mg/dL)	5(11.9%)
Low FEV1(<70%)	9(21.4%)
Diabetes	6(14.3%)
Chronic AF	5(11.9%)
Peptic ulcer	4(9.5%)
Parkinson disease	1(2.4%)
>1 comorbidity	9(21.4%)

Legend: COPD: chronic obstructive pulmonary disease; CVE: cerebral vascular event; FEV1: forced expiratory volume in 1 second; AF: atrial fibrillation.

Results

Twenty-five patients (60%) had a right-sided procedure, 17 patients a left-sided procedure (40%). Eight patients (19%) underwent limited resection as segmentecomy or wedge resection, 25 patients (59.5%) had lobectomy, 2 patients (4.8%) had bi-lobectomy, 6 patients (14.3%) had pneumonectomy (2 right, 4 left) and one (2.4%) had completion right pneumonectomy. Eight patients (19%) underwent extended resection (3 left-atrial resection, 5 chest wall resection and reconstruction). Six patients received post-operative radiotherapy and 8 patients received post-operative chemotherapy.

Histological definition was undertaken according with the WHO criteria for classification of NSCLC (7). Histological diagnosis showed a prevalence of adenocarcinoma (20/42pts, 47.6%) followed by squamous cell carcinoma (12/42pts, 28.6%) and other tumors (5/42pts, 11.9%) as carcinoids and large-cell carcinomas. Five patients had stage pIIIA with nodal staging pN_1 (4 patients T_4-N_1 9.5%; 1 patient T_3-N_1 2.4%). All the other patients were classified as pIIIA because of pN_2 nodal disease. Neither of our patients had a bulky N_2 involvement found at surgery ($pIIIA_4$). The majority of our patients had a micro-metastasis N_2 involvement ($pIIIA_1$ 88%) or a single station N_2 disease ($pIIIA_2$ 12%). Five patients (13.5%) with pN_2 micrometastasis disease were pN_1 free.

The in-hospital mortality was 9.5% (4/42pts). The causes of death were two bowel ischemia, one post-operative acute myocardial infarction and one Acute Respiratory Distress Syndrome (ARDS) in a right-pneumonectomy with bronchus-pleural fistula. Pneumonectomy, and poly-vasculopathy were statistically significant predictors of in-hospital mortality (Table 2). The overall post-operative morbidity rate was 59.5% (25/42pts). Nine patients (21.4%) suffered of more than one complication. The major complication type and rate were reported in Table 3. Pneumonectomy, extended resection, pre-operative atrial fibrillation (AF) and lower FEV_1 were associated with an increasing risk of post-operative complications (Table 2).

The mean follow-up time was 28.32±19 months (range 5-103). The overall mortality during the follow-up period was 68.4%. We had one long-term survival (103 months) 78-year-old man, ex smoker without other comorbidities. He was staged as cIIB ($T_2bN_1M_0$) and underwent a right upper lobectomy. The pathological stage was pIIIA ($T_2bN_2M_0$). Because of the age he was not treated with adjuvant therapy. Until now is still alive, in good clinical condition without signs of tumor recurrence. The overall survival was 73% at 1 year, 23% at 3 years and 16% at 5 years (Fig. 1). The median survival of all patients was 20.7±4.8 months. Twenty-two (57.9%) patients had disease recurrence and it was the cause of death in 21 patients (55.3%). Disease recurrence was local in

TABLE 2 - PREDICTORS FOR IN-HOSPITAL MORTALITY AND MORBIDITY AT THE BINARY LOGISTIC REGRESSION.

Variables	RR	95% CI	p-Value
Predictors for in-hospital mortality			
Pneumonectomy	9.8	1.6-53.4	0.006
Polivasculopathy	6.1	1.3-26.7	0.02
Predictors for post-operative complications			
Pneumonectomy	13.9	2.0-65.3	0.001
Extended resection	10.2	1.8-55.7	0.004
Pre-operative AF	3.3	1-16.8	0.043
Low FEV1	4,7	1.1-22.4	0.033

Legend: RR: relative risk; CI: confidence interval; AF: atrial fibrillation; FEV1; forced expiratory volume in 1 second.

TABLE 3 - POST-OPERATIVE COMPLICATIONS.

Complications	Patients	
	n	%
Post-operative AF	13	30.9
Prolonged air-leak	8	19
Pneumonia	4	9.5
Acute renal failure	3	7.1
Stroke	2	4.8
Delirium	2	4.8
Bowel ischemia	2	4.8
Post-operative AMI	1	2.4
Post-operative bleeding	1	2.4
Bronchus-pleural fistula	1	2.4
ALI/ARDS	1	2.4

Legend: AF: atrial fibrillation; AMI: acute myocardial infarction; ALI/ARDS: acute lung injury/acute respiratory distress syndrome.

12 patients (31.6%) and distant in 10 patients (26.3%). The mean time of recurrence free survival was 13.2±5.9 months (range 4-24 months). Five deaths were not related with cancer (3 cardiovascular, 2 traumatic). The only risk factors for long-term mortality at the multivariate analysis were recurrence of disease (p=0.017; RR 22.4 95% CI 13.9-27) (Fig. 1). No difference was found between $pIIIA_1$ and $pIIIA_2$ in term of prognosis (p=0.86). Performance status of survivals at the follow-up was 2.8±0.7 (p=0.08).

Discussion

The series herein reported represents a selection of older patients with NSCLC in which N_2 disease was found at the time of pathological staging. The majority of these patients (33/42 pts 78.6%) were evaluated and treated in the era before the advent of more advanced diagnostic tool such as PET-CT scan. In that period

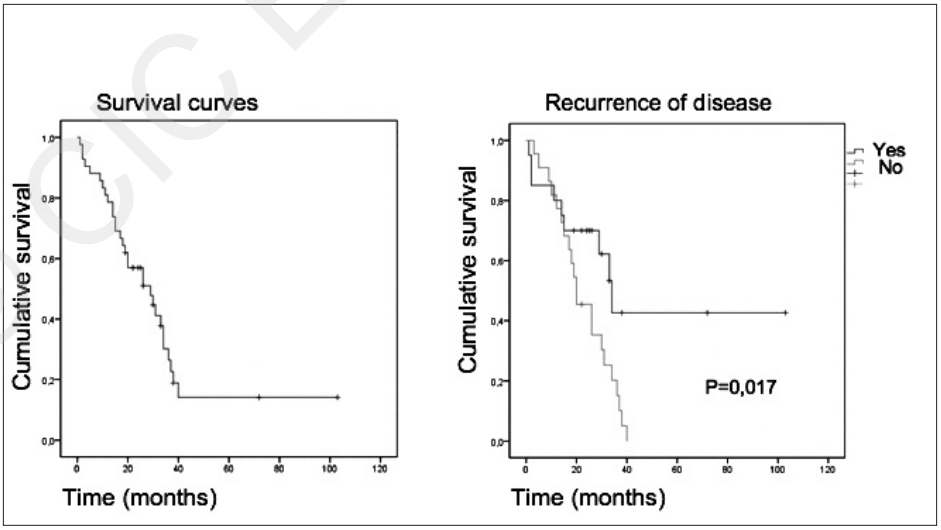

Fig. 1 - Long-term survival curves using the Kaplan-Meier method. On the left has been reported the overall survival and on the right the actuarial survival according to recurrence of disease (long-rank test).

(2000-2005) all patients referred for surgery at our departments undergoing a careful work-up in which the mediastinal lymph nodes evaluation with CT-scan was one of the most important steps. Patients with mediastinal lymph nodes enlargement more than 10mm in the short axis were further staged by standard medistinoscopy. Reviewing the literature the chest CT-scan shows a sensitivity of 57%, specificity of 82%, a positive predictive value (PPV) of 56% and a negative predictive value (NPV) of 83% (8). On the other hands, standard mediastinoscopy shows a sensitivity of 81% a specificity of 100%, NPV of 91% and PPV of 100% (8-10). Mediastinoscopy is an invasive procedure, performed under general anesthesia, with an existence, even minimal, operative risk also in experienced hands (11). For these reasons we were reluctant to offer mediastinoscopy in older patients with associated comorbidities when the CT-scan was negative and the suspicion of N_2 disease was minimal.

After the advent of PET/CT-scan all patients, even without nodal enlargement on the CT-scan, were evaluated by PET/CT-scan. Mediastinoscopy was applied in patients with PET positive lymph nodes. Nowadays we know that PET/CT-scan give about 93% of NPV and 79% PPV (8,10). Comparing medistinoscopy and PT/CT-scan the sensitivity and NPV of both procedures are similar, but PPV and specificity of PET/CT are lower than those of mediastinoscopy due to the false positive PET evaluated nodes in inflammatory process (10). In a prospective study Cerfolio et al (12) reported that after medistinoscopy and EUS mediastinal staging unsuspected or non-imaged N_2 disease was found only in 2.9% and 3.7% of patients respectively. They don't recommend the routine use of mediastinoscopy and EUS in the preoperative work-up (12,13). In our experience the incidence of occult pN_2 disease in 274 patients older then 75 years is of 13.6% that became 4.1% after the PET/CT-scan advent.

Recently we introduce in our clinical practice the use of EBUS and EUS. The last two techniques have a sensitivity and specificity of 93% and 91% respectively in experienced hands with a PPV of 98% but still a NPV of 77% (10,12). Moreover EBUS/EUS are less invasive, safer, and cost-effective compared with mediastinoscopy (9,14,15). In our opinion all this aspects are not negligible in elderly patients. We expect that the routinely application of EBUS/EUS techniques during staging of mediastinum in our institutes may reduce further the incidence of occult pN_2 disease in the next future.

In literature the treatment of stage IIIA(N_2) is still in a gray zone in between operable stages such as stage IA-IB and IIA-IIB and inoperable stages such as stage IIIB and IV (2,4,16,17). Many reports showed a 5-year survival for surgically treated stage IIIA ranging from 8.9% to 53% (2-4,18,19). When N_2 disease is discovered before thoracotomy many groups are in favor of multimodality treatment (1,15,16,18). Recently N_2 disease has been divided in different entities based on the number of involved station, the presence of micrometastases, or bulky disease (2,5). In literature has been reported a prognostic implication of this subgroups differentiation of IIIA N_2 disease (5,18,20-22). Older patients with N_2 disease seems to have a poor prognosis compared with younger N_2 patients as reported by different authors (18,23,24). Voltolini et al (25) in the 2009 advocate no surgery for octogenarians with stage IIIA NSCLC. There are many reasons to explain the poorer survival of older patients with stage IIIA N_2. Older patients cannot tolerate extended surgical procedures because of comorbidities, poor respiratory function and less physiological reserve. In our series the overall in-hospital mortality was 9.5% similar to the literature results (1,18,23-25). Nevertheless our mortality rates after pneumonectomy was 28.6%. In other series operative mortality in older patients underwent pneumonectomy ranging between 7.5 to 25% (24,25). According to other authors we believe that the surgeon should made every efforts to avoid pneumonectomy in older patients and if the preoperative risk to need pneumonectomy is high the patient should not be considered for surgery. On the other hands older patients with suboptimal performance status were frequently treated with limited surgical resection such as wedge or atypical segmentectomy without radical lymphadenectomy. This can explain the high incidence of local recurrence and poor long-term survival. Lobectomy and radical lymphadenectomy even in older patient had acceptable risk as reported by many authors and it is the gold standard surgical procedure for lung cancer resection (2,25). In our experience we had a lobectomy and bilobectomy in-hospital mortality of 7.4%.

Oncologists are reluctant to treat older and sicker patients and chemotherapy could be poorly tolerated. This also probably contributes to the poor long-term survival of older N_2 patients (1). The older patients sometimes are less motivated or physical limited in performing pulmonary rehabilitation, therapy and cancer follow-up than younger people. Generally we are not in favor for surgery in older people (>75years) with clinical stage IIIA(cN_2). Only in selected cases with a good performance status and minor comorbidities we consider surgery but only after neoadjuvant therapy. If the patients cannot tolerate chemotherapy may be cannot tolerate surgery as well. In our experience pneumonectomy is a risk factor for in-hospital mortality (p=0.006) and morbidity (p=0.001). Extended resection is a risk factor for in-hospital morbility (p=0.004). This aspect highlights the fragility of these patients and that

a good preoperative performance status is mandatory to select older patients for surgery. Indeed despite a preoperative "selection of candidate" we observed a worsening of performance status after the operation due to chronic pain (32%), shortness of breath (22%), orthopedic problems (36%) and other (10%) with a trend towards the statistical-significance (p=0.08). Other factors related with in hospital mortality and morbidity are poli-vasculopathy, preoperative AF and low FEV_1 reflecting the complexity of these patients. The patients herein reported were incidental findings of occult N_2 disease. According to other series (17,23-25) pN_2 disease in older patients gain disappointing results. In our series the 5-year survival is only 16% by far from the 24% 5-year survival reported by Goldstraw et al for stage pIIIA in the seven edition of the TNM staging (20). Moreover our experience said that the majority of our patients death for cancer recurrence (55.3%) and not because reduced life-expectancy or comorbidity, only the recurrence of the disease (p=0.017) was correlated with poor survival.

Conclusion

We learn that in older patients potentially operable we need to make every efforts to exclude N_2 involvement. CT-scan and PET/CT-scan evaluation are mandatory, but even in case of negative lymph nodes at the imaging studies we must exclude false negative cases using invasive mediastinal staging process. A good alternative to mediastinoscopy could be EBUS and/or EUS in experienced hands (9,10). Only in case of negative invasive mediastinal staging these patients were considered for surgery. All these efforts should be guided by the poor results that surgery alone offers in older patients with pIIIA(N_2) stage NSCLC. In the future it is advisable to careful review all the results coming from well design randomized trial and registry results to give the best treatment options for older patients affected by NSCLC in term of quality of life and survival advantage. Further study needs to understand if different patterns of N_2 involvement could have an impact on treatment choice and prognosis also in older patients.

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