Original Paper

Recurrence in patients that underwent surgery for lung cancer

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SUMMARY
INTRODUCTION: The recording and analysis of lung cancer recurrences in patients with primary non-small cell lung cancer that initially underwent radical surgical treatment. **METHOD:** This is a retrospective study that deals with the occurrence of lung cancer recurrences through systematic postoperative follow-up of 350 Greek patients with primary non-small cell lung cancer for 5 years. All of these patients underwent radical surgical treatment in the same Thoracic Surgery Department in the period 1995-2010. **RESULTS:** Of the 350 patients, 308 were male and 42 female, 50% had adenocarcinoma, 40% squamous cell lung carcinomas, 8% undifferentiated large cell lung carcinomas, and 2% mixed type of adenosquamous lung carcinomas. A total of 350 interventions were performed, of which 158 were lobectomy, 42 bilobectomy and 150 pneumonectomy. Of the 350 patients, 130 experienced relapse within five years of which 31 were diagnosed with local relapse, 65 with distant metastases and 34 with a combination of both.
Pneumon 2017, 30(3):133-140.

INTRODUCTION

It is well known that Lung Cancer is now the leading cause of cancer death for both males and females being responsible for 20% of cancer related deaths worldwide[1]. The total number of patients dying from lung cancer outranges the number of patients dying from breast, prostate and bowel malignancies altogether[2]. Every year 1.800.000 new cases of lung cancer are diagnosed, causing 1.180.000 deaths yearly. In the U.S.A. 210.000 new patients with lung cancer are diagnosed every year causing 157.000 deaths whereas in Europe there are 400.000 new cases each year[3]. According to unofficial records released by the Oncology Department of 3rd University Medical Clinic of "Sotiria" Hospital, 2000 new cases of lung cancer are grossly diagnosed in Greece yearly with 10.000 doctors from various specialties involved with their care such as Chest Physicians, Oncologists, Thoracic

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Surgeons, Radiotherapists, Pathologists etc.

Only a 15-20% of those patients are eligible to undergo surgical therapy with the vast majority of them receiving chemotherapy and radiotherapy[4]. Surgical resection is the only type of treatment with curative intent and can without any doubt , prolong survival and improve quality of life for these patients[5]. One of the few weaknesses of surgical treatment for lung cancer is the possibility of cancer recurrence, appearing either locally at the area of operation or distally to the initial primary lesion[6-8].

All stages of lung cancer should be considered for surgical treatment if certain criteria are fulfilled[9]. Stages I and II have absolute indication for resection, stage III can sometimes be operated, whereas stage IV is rarely operable[10]. Patients that are initially subjected to surgical resection of cancer are always under regular follow-up for at least 5 years because of the following reasons:

1. Identifying any early or late complications that can occur postoperatively.
2. Determine the disease free interval in case of disease recurrence.
3. Determine the overall survival postoperatively.
4. Identify any disease recurrence.
5. Diagnose any second or metachronous primary cancer[11].

AIM

A brief review of the literature on this topic reveals no studies reporting lung cancer recurrence post-surgery in Greece. Main goal of this study was to report and analyse results of data collected from lung cancer recurrences postoperatively through a systematic and thorough follow-up of patients with primary non-small cell lung cancer who were initially operated with curative intent from the same surgeon at "Sotiria" Athens Chest Diseases Hospital .

This study was mainly conducted to evaluate current data on lung cancer recurrences postoperatively and investigate the biological pathways thought to be responsible for cancer recurrence[12]. Secondary this study identifies methods for early detection of tumor recurrence and suggests possible prognostic factors for resected lung cancer recurrence. Finally all the necessary clinical tests for the evaluation of fitness for surgery and the most common surgical methods are mentioned.

MATERIALS AND METHODS

Three Hundred and fifty patients (350) in total were enrolled in this study. All of them were operated by the same surgeon at the Thoracic Surgery Department of "Sotiria Regional Chest Diseases Hospital", Athens, Greece, during a time period of 15 years (1995-2010). Eligible patients were initially treated with surgery for primary Non Small Cell Lung Cancer and were systematically followed-up for at least 5 years postoperatively[13]. Depending on the decision of a Multi-Disciplinary Oncology Meeting following surgery, doses of adjuvant chemotherapy or radiotherapy were administered to the patients who would benefit from adjuvant therapy.

In the present study only major lung resection procedures were included, meaning lobectomies and pneumonectomies. Mini resections such as wedge excisions and segmentecomies were excluded from this paper[14-16]. Patients did not have a routine PET scan prior to surgery, because Patient recruitment started in 1995 and ended in 2010.

All patients were operated under general anaesthesia and intubated with double lumen tube to achieve isolation of the operated lung. Patients with central tumors underwent rigid bronchoscopy at the beginning of the operation for re-evaluation of the endobronchial extend of their disease. A typical posterolateral thoracotomy approach was applied with resection of the lung parenchyma involved by the tumor (lobectomy, bilobectomy or pneumonectomy), followed by systematic mediastinal lymph node sampling[17,18].

The systematic follow-up was conducted by the operating surgeon following guidelines from EACTS and ACCP[19], taking under consideration the characteristics of the Greek National Health System , demographics and location of each individual patient.

Each follow-up appointment included documentation of patients medical history and a complete physical examination of each one of them[20,8]. A routine chest X ray was done 15 days, 1 month, 4 months, 9 months and 12 months post surgery. At the time of 1 year postoperatively, a CT scan of the Thorax was performed, a full set of blood tests including cancer serum markers, as well as a flexible bronchoscopy for visual examination of the bronchial stump and cytology specimen examination of bronchial washing and brushing.

During 2nd and 3rd year of follow-up , patients medical history, complete physical examination and chest Xray was conducted every 4 months while CT scan of chest

and upper abdomen was repeated every 6 months. For the 4th and 5th year post surgery patients medical history, complete physical examination and chest Xray was conducted every 6 months while CT scan of chest and abdomen repeated yearly.

Between patients follow-up appointments if any symptom or radiographic study was suspicious for recurrence, a complete focal workup was done trying to confirm the diagnosis[21]. If cancer was detected and proven after tissue diagnosis then the patient was referred to a Multi Disciplinary Oncology Meeting. The MDT decided on whether it was lung cancer recurrence or a second primary and which should be the optimal treatment plan. According to the MDT decision, patient received chemotherapy with or without radiotherapy or were referred back to the surgeon[22]. The surgical options were completion pneumonectomy of the remaining lung parenchyma or metastatectomy of the tumor wherever that was technically feasible.

The systematic review of literature was conducted using data from U.S. National Library of Medicine through pub med website. Key words that were used for this search were: *recurrence in patients with NSCLC*, *recurrence in patients with NSCLC after surgery*, *local and distant failure lung cancer*, *recurrence patterns NSCLC*. All studies were reviewed and studies non relevant to the topic were excluded from review. A simple statistical analysis was performed , mainly using mean and median values of documented data. This study was approved by the Scientifical and Ethical Committee of this Hospital for the collection and analysis of patients data operated in this department.

RESULTS

All 350 patients in total that were enrolled in this study were initially operated with curative intend for Non-Small Cell Lung Cancer in Thoracic Surgery Department of "Sotiria Regional Chest Diseases Hospital", between the years 1995-2010. The same surgeon performed all surgical procedures and conducted the patients systematic follow-up and documentation of relevant data. Patients that required adjuvant therapy[23] were treated at the Oncology Department of 3rd University Medical Clinic of "Sotiria Athens Chest Diseases Hospital". In case of cancer recurrence patients were discussed at the Multi-Disciplinary Oncology Meeting with chest physicians, oncologists and the operating surgeon to determine optimal treatment strategy[22]. Lung cancer staging was based on the 6th revision of the TNM staging system that was in use until the beginning of 2010[24].

Two Hundred and eight patients (280) out of the 350 in total were male with ages ranging from 42 to 82 (mean age 59). Male to female ratio was 7 to 1. Tumor histology was: 175 lung adenocarcinoma (50%), 140 squamous cell lung carcinomas (40%), 28 undifferentiated large cell lung carcinomas (8%) and 7 mixed type of adenosquamous lung carcinomas (2%).

Disease staging was found as follows:

Stage I 118 patients: IA (T1N0) 38 patients, IB (T2N0) 80 patients

Stage II 146 patients: IIA(T1N1) 18 patients, IIB(T2N1) 85 patients

Stage IIIA 86 patients: (T3N1) 21 patients, (T2N2) 45 patients, (T3N2) 20 patients

Most common Lung cancer stage was IIB (T2N1) with 85 patients (24.3% of total number pf Pt), followed by IB (T2N0) with 80 patients (23%) and IIIA (T2N2) with 45 patients (13%).

Three Hundred and fifty (350) operations in total were conducted as follows:

- 158 Lobectomies
- 42 Bilobectomies
- 150 Pneumonectomies.

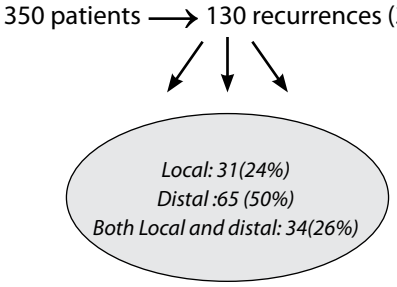
Of the 150 pneumonectomies 92 were done at the right side and 58 at the left while 120 of them were typical and 30 intrapericardial.

Most common procedure was the right upper lobectomy, whereas 22 out of 42 bilobectomies were upper (upper and middle lobes) and the other 20 were lower (middle and lower lobes)

All procedures included a systematic mediastinal lymph node sampling. This procedure was preferred because of the similar oncological results according to current literature (ACOSOG Z0030 study)[25] as it is reported to have similar overall survival and seems to be superior than mediastinal nodal dissection in terms of surgical time and complications[26].

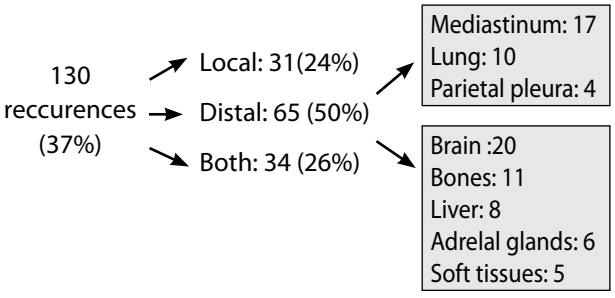
One hundred and thirty (130) out of the 350 patients (37%) were diagnosed with disease recurrence during the first 5 years of follow-up[27]. Type of recurrence varied between local, distal metastases or both. The vast majority of recurrences (110 patients-90%) occurred in the time period of 18 to 36 months post-surgery. Out of the 130 patients found with recurrence: 31 (24%) had local recurrence, 65 (50%) had distant metastases and 34 (26%)

had both. Twelve patients were diagnosed with a second metachronous lung primary cancer thus all of them were excluded from this study.



Among all cases of local recurrences, 17 patients had mediastinal disease recurrence, 10 within lung parenchyma and 4 on the parietal pleura[28].

Distant metastases were located in the brain for 20 of the cases, in the bones for 11 cases, in the liver for 8 cases, in adrenal glands for 6 of the cases and for 5 of the cases in soft tissues.



Thirty four patients developed both local and distance recurrences of disease. Out of those there were 13 with combined lung and brain secondaries or combined lung and adrenal gland lesions with mediastinal involvement in some of those cases.

DISCUSSION

Despite the fact that surgical treatment of early stages I and II is done with curative intent, it is well known that a considerable number of patients (30% to 50%) develop disease recurrence postoperatively and eventually die of this[29]. Therefore a question arises why someone with early stage lung cancer that underwent radical surgical resection with both macroscopically and microscopically free resection margins (R0 Resection), develop disease recurrence.

The development of post-surgery recurrence could physiologically be explained through the following 2 pathways:

1. Existence of micro metastatic disease at the time of surgery

This is disease that is not clinically evident (lesions with diameter of 0,2-2mm with an optical microscope of 5x) that is caused by solitary cancer cells (occult micro metastatic cells <0,2mm), which travel from the primary lesion through the blood stream to a distal site[30,31]. If those cells manage to survive at the microenvironment of that distal site, they divide and grow forming a metastatic tumor[32]. On the other hand any lesion identified at optical microscopical examination with size larger than 2mm is consider as a satellite tumor.

It is very likely that those occult metastases existed from the time of surgery but all available classic imaging tests (CT, MRI, Bone scan) as well as the biological imaging tests (PET Scan, PET CT) for staging of lung cancer were not able to identify those lesions due to their size. Tumor cells that could have been identified at the time of surgery are those circulating in peripheral blood stream (CTC – circulating cancer cells) or tumor cell deposits within the bone marrow or locoregional lymph node stations. CTC existence is still a field of debate and is still not clear if they represent a bad prognostic factor of tumor recurrence. Bone marrow microscopical tumor deposits is also not clear if can be considered as true bone metastasis. In current literature there is no clear evidence of correlation between CTC presence and reduced Lung cancer survival.

2. Dissemination of tumor cells from primary tumor (DTC)

During manipulations upon lung parenchyma that are necessary for lung resection some tumor cells might disseminate from primary lesion and spread through the blood stream. This is the main reason why some surgeons suggest that division of the pulmonary vein related to the tumor lobe (vessel that drains blood from the tumor) should be done first and prior to division of pulmonary artery (vessel that perfuses lung parenchyma with the tumor) when operating on lung cancer so that the spread of DTC risk is reduced. It is easy to conclude that DTC can cause disease recurrence at a later time than CTC[33].

Most of lung cancer recurrences post-surgically (90%) appear during the first two years postoperatively. They can occur either locally or distantly to primary tumor and most of the times are lethal within 1 year from the time of their diagnosis. The term local metastasis or local recurrence is defined as tumor growth at the surgical resection margins (bronchial stump, fissure, vessel stumps), at lung hilum or mediastinum[34]. All other metastasis are considered as

distal metastases or recurrences. It is of great importance to define the type of metastasis (local or distal) in all studies investigating post-surgical recurrences of primary lung cancer and when this event was diagnosed if both types coexist and which one appeared fist. On top of that it is important to exclude cases of second metachronous primary lung cancers.

One interesting question that arises is whether prognosticators for tumor recurrence of patients operated for primary lung cancer with curative intent exist[35]. A review in relevant literature reveals that those prognosticators can be classified into two categories:

1. Factors of classical determination that are related with TNM staging system of primary tumor

Tumor diameter (>3cm and >5cm), presence of N1 or N2 involvement, advanced TNM stage, presence of symptoms, bad patients performance status, cessation or not of smoking, high SUV values on PET /CT, low tumor differentiation on pathology examination, less than lobectomy resection, invasion of blood vessels and lymphatics within tumor, invasion of visceral pleura, microscopically positive resection margins (R1) and neglect ion of typical lymph node dissection or systematic sampling as well as adjuvant chemotherapy or radiotherapy administration postoperatively[36-38].

2. Factors that can be identified with molecular biology techniques

It is very well known that lung cancer is an aggressive type of neoplasm that has many histological subtypes, each one of them with different molecular biology characteristics[39]. The clinical behaviour of the tumor is related to many genetic alterations related to cell cycle and cell division, apoptosis, mutations, chromosomal dislocations and angiogenesis[40,41].

Another logical question arises next: **Is there a way to prevent recurrences post primary lung cancer surgery from happening, delay them or reduce their extend?**

Means that we have so far are well-established: Induction chemotherapy (doses of chemotherapy administered prior to surgery), adjuvant chemotherapy (doses administered days or weeks post-surgical treatment), adjuvant radiotherapy and quite recently developed targeted molecular drug therapy. The role of chemotherapy either in form of induction or adjuvant treatment has been thoroughly investigated over the last years so that we are now aware of pros and cons of each one of those, and the overall survival benefit to the patient which is around 5% in 5 years' time[42,23].

Today, there is no question that chemotherapy is of great importance for the patient, regardless if it is in form of induction or adjuvant treatment, as long as patient receives it[43]. The fact is that almost 90% patients could undergo induction chemotherapy, but only a 60% of them could receive adjuvant chemotherapy because of various reasons. Someone could conclude that if adjuvant chemotherapy could be administered in larger proportion of patients then survival benefit would outrange survival benefit from induction chemotherapy.

It is of general agreement that adjuvant radiotherapy, usually received by patients with N2 disease, also known as "mediastinal lymph node sterilization" is important for local disease control but there are no evidences of increasing overall survival[44].

In the near future it is more than clear that individualized molecular targeted drugs will play a very important role in prevention of metastases development post surgically and will change the natural history of disease recurrences. Targeted treatment in lung cancer is mainly classified into two categories : inhibitors of intracellular Epidermal Growth Factor Receptor (EGFR) and monoclonal antibodies targeting extracellular receptor of Vascular Endothelium (VEGF)[45].

Tyrosine Kinase Inhibitors (Erlotinib, Gefitinib, Giotrif etc.) are targeting cancer cell intracellular receptor by blocking receptor phosphorylation, thus blocking cell cycle and cellular division of cancer cells and inducing apoptosis[46].

Bevacizumab is a monoclonal antibody that binds on VEGF and inhibits VEGF biological pathway, blocking angiogenesis and stops tumor growth[47].

Immune therapy in lung cancer is based on principles of immune reaction against an unknown antigen to the human body. More specifically, when a foreign antigen like a cancer cell for instance, is detected, two main defence systems are activated: natural and acquired immunity. Natural immunity is the first defence line after a bacterial od cancer cell invasion. There are many types of cells involved in natural immune system like macrophages, natural killer cells that bind to the cancer cells and destroy them and dendritic cells. Dendritic cells are antigen – presenting cells that detect foreign antigens and present their peptides to other cells of the immune system. At a later stage dendritic cells present antigen peptides to the lymph cell system (T and B lymphocytes) and this is how acquired immunity is developed. This

type of immunity if very target-specific because of the T and B receptors that identify specific antigen peptides[48].

Once T lymphocytes are activated through dendritic cells inside a lymph node, they travel through blood stream to detect and destroy any intruder like a cancer cell. T lymphocyte activation from dendritic cells is achieved through 2 steps (signal 1 and 2). During those steps surface antigens of T lymphocyte and dendritic cell come in contact and identify each other.

According to current practice lung cancer patients will receive cisplatin based chemotherapy as indicated. Adjuvant chemotherapy is mainly administered to the subgroup of patients that have lymph node involvement or tumor greater than 4 cm in diameter. At the moment the use of targeted molecular treatment and immune therapy as an adjuvant to surgery with curative intent for early stage lung cancer is under investigation, as a very high proportion (up to 50%) of patients receiving radical lung cancer resection eventually develops disease recurrence.

A recent Phase II trial that investigated the benefit of adding bevacizumab to adjuvant chemotherapy in early stage lung cancer patients that received chemotherapy post-surgical treatment had disappointing results. According to the Eastern Cooperative Oncology Group 1505 study, 1500 patients that were operated because of lung cancer stage IB, II, IIIA were randomized post-surgery and underwent 4 cycles of platinum based chemotherapy with or without adding bevacizumab. Final result of study is that there was no significant difference observed in overall survival in the two groups of this study (Hazard ratio 0.98 , p value: 0,75).

RADIANT study has evaluated the role of Erlotinib in adjuvant treatment of patients with EGFR mutation that were operated for early stage non-small Cell lung cancer. Final results showed no improvement in disease free survival between the Erlotinib group and the placebo group (hazard ratio 0.9, p 0.324)[49,50]. Similar studies are running at the moment in Asia for such patients positive to EGFR mutations .

As for the role of immune therapy in adjuvant treatment of patients operated for early stage non-small Cell lung cancer, various studies have been conducted worldwide. MAGRIT study, that was an international double blind randomized study, has recently announced its results, where it's been shown that Adjuvant treatment with MAGE-A3 adjuvant immune therapy did not manage to increase disease free survival, compared to placebo treatment in patients that express gene 3 – MAGE family gene.

National Clinical Trials Network located in U.S.A. is conducting a clinical trial (ALCHEMIST STUDY) investigating molecular targeted drugs as adjuvant therapy in stage IB, II, IIIA lung cancer patients that received surgical treatment with curative intent. Postoperatively , patients have a full molecular profile test done, including EGFR mutation and ALK translocation presence. Following the positive patients for the above molecular tests the proper target inhibitor is administered, or a placebo drug. For the patients without those mutations (EGFR-, ALK-) after giving systematic chemotherapy, Nivolumab immune therapy follows or just observation.

This study is offering dep gene analysis on all patients enrolled, in order to clarify the molecular parameter that favours disease recurrence or sensitivity on specific antineoplastic agents of adjuvant chemotherapy.

Finally, Phase II and III clinical studies are running, comparing combination of surgical treatment after induction chemotherapy or before adjuvant therapy with molecular targeted drugs instead of conventional chemotherapy. The Western Japan Oncology Group phase III randomized trial is such a study that compares surgical treatment of stage II, IIA non-small Cell Lung Cancer, combined either with adjuvant chemotherapy (Gefitinib) or with tyrosine kinase inhibitors (TKI's) if patients are positive for EGFR mutation[51]. It is obvious that more studies are needed on targeted therapies before or after surgical treatment, so that there will be solid evidence on their effectiveness.

DISCUSSION

Unfortunately, it is a very unpleasant reality that lung cancer patients that underwent surgical resection have a high recurrence rate. It is still a fact that surgical resection is the only treatment strategy with curative intent, as chemotherapy and radiotherapy are as it is well known, adjuvant or/and palliative treatment strategies. Surgical therapy of early stage lung cancer appears to correlate with very low recurrence rates, and on the other hand, the more advanced lung cancer is , the recurrence rate is higher, although not proporti onally.

On top of all that, the well-known and established prognostic factors are playing important role in disease recurrence and overall survival. Factors that are related to molecular biology cancer pathways are a relatively new weapon in diagnosing and can clarify many aspects of biological tumor behaviour and define, up to a certain level, response to treatment. As for the role of targeted molecular therapy and immune therapy in adjuvant

treatment of early stage Non-Small Cell Lung Cancer, the international scientific community is investigating their effectiveness in increasing overall survival as the recurrence rate of lung cancer, post complete surgical tumor resection, is reportedly up to 50%.

Fighting lung cancer seems to be a problem for many years to come, especially if smoking still remains a bad human hobby. This fight that is involving many different medical specialties with various treatment strategies that can be followed, has to be fought with great caution and alignment to the international guidelines with reassurance that this practice with be individualized to each every patient. Undoubtedly a complete clinical investigation of such a complex biological procedure as lung cancer recurrence, demands a multi-disciplinary approach of doctors with various specialties such as oncology, pulmonology, radiology and thoracic surgery.

Finally a special interest has to be shown on strict and regular follow-up of patients with lung cancer, that has to be systematic and thorough, since it is a sine-qua-non feedback factor, of every treatment method and practice for the clinician doctor.

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