

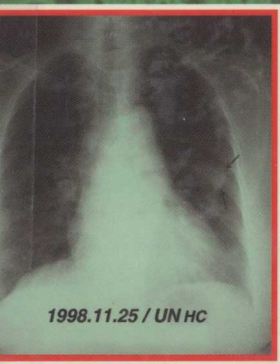
肺癌臨床手冊

inical Handbook of Lung Cancer

主編：吳懷申

Editor-in-Chief:

Huai-Shen WU, MD, FCCP



1998.11.25 / UN HC

ISBN 99937-630-0-4

MACAU
2001

R734. 2-62

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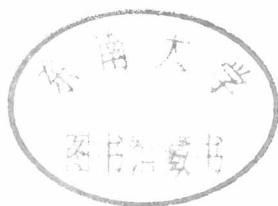
(中英文對照版)

CLINICAL HANDBOOK OF LUNG CANCER

(Chinese-English Bilingual Edition)

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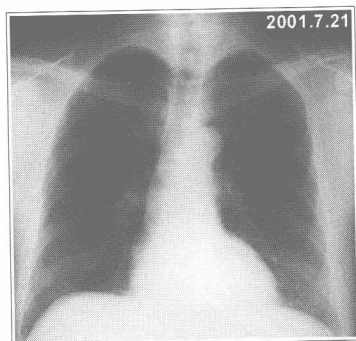
Editor-in-Chief: **Huai-Shen WU, MD, FCCP**



SEU 06663798

澳門特別行政區政府衛生局
Serviços de Saúde da R.A.E.M.

Macau, 1st September 2001



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Clinical Handbook of Lung Cancer

吳懷申 主編

澳門特別行政區政府衛生局 出版 發行

澳門華輝印刷有限公司 製版 印刷
(澳門漁翁街 82 號南豐工業大廈三樓 B 座 電話: 00853-337972)

32 開本 8.75 印張 20 萬字
2001 年 9 月 第一版 第一次印刷
印數 1800 冊

ISBN: 99937-630-0-4

獻給培養我們的老師
同事和青年醫生

全體作者敬獻，2001年9月

*To Our Dear Teachers, Colleagues
And Young Doctors,*

From All Authors, September 2001

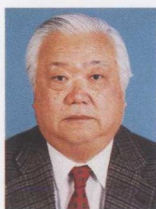
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（澳門仁伯爵綜合醫院建院於1874年，有127年歷史）

Preface

Lung cancer is the most common malignant tumor in the world today. The incidence and mortality of lung cancer has shown significant increase in industrial countries in the last 20 years. In terms of geography, the highest incidence in males was seen in Eastern Europe (78.9/100 000 population), while for females in North America (32.9/100 000). The highest mortality in males was seen in Hungary (84.0/100 000) and in the United States in females (26.3/100000). Lung cancer should therefore be the primary object of prophylaxis and treatment among all the different kinds of malignant tumors.

The *Clinical Handbook of Lung Cancer* is an extremely useful clinical handbook for those setting out to treat this tragic disease. It should contribute to the early detection, early diagnosis and early treatment of this disease, all of which are necessary in order to increase 5-year survival rate.

The Editor-in-chief, Professor Huai-Shen Wu, is not only a respected senior thoracic surgeon and oncologist, he is also the son of my late friend Professor Shang-Fang Wu, who was also an extremely famous thoracic surgeon and oncologist not only in his native China but also throughout the world. Professor Huai-Shen Wu worked with my staffs in 1987 in Tokyo Medical College Hospital, and there was excellent interchange of information and teaching between them. In 1996, Professor Huai-Shen Wu published the LUNG Principle for the surgical treatment of lung cancer and I feel that this viewpoint is correct. I am sure that Professor Wu will continue to make even more contributions in Macau.



Professor Emeritus **Yoshihiro Hayata**, M.D., Ph.D., FRCS (Eng.)

President, 2000 World Conference on Lung Cancer

Past President, IASLC, 21st July, 2001

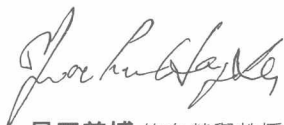
早田序言



肺癌是當今全球最常見的惡性腫瘤。近二十年來，在工業發達的國家中，肺癌的發病率和死亡率始終在上升。全球男性肺癌發病率最高的地區是東歐地區(78.9/10萬人口)，女性是北美地區(32.9/10萬人口)；男性肺癌死亡率最高的國家是匈牙利(84.0/10萬人口)，女性是美國(26.3/10萬人口)。因此，肺癌一直是全球惡性腫瘤中防治的重點。

澳門特區衛生局出版發行的【肺癌臨床手冊】是一本很有用的臨床手冊，特別有益於臨床醫生早期發現、早期診斷和早期治療肺癌，從而真正達到提高肺癌的五年生存率。

主編吳懷申教授不僅是一位受尊敬的胸外科和腫瘤學資深醫生，也是我最好的中國朋友、已故吳善芳教授的長子。吳善芳教授是中國和世界上著名的胸外科和腫瘤學專家。1987年，我資助吳懷申教授來日本東京醫科大學研修胸外科，在工作中他與我的同事們進行了很好的學術交流。1996年，吳懷申教授提出了肺癌外科治療的LUNG原則，我很同意他的觀點。我真摯希望他在澳門期間，為澳門地區的胸外科和腫瘤外科做更多的貢獻。



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2001年7月21日 日本東京

Author's Preface

Cancer is different from AIDS and other infectious diseases that can't be controlled by life style or action of human life. Early detection and radical treatment of cancer are still difficult now.

During the twentieth century, cancer research indicated that cancer was related with eight major factors, i.e. (1) Human ageing; (2) Life style; (3) Psychogenic factor; (4) Hereditary factor; (5) Nationality and sex; (6) Geography and climate; (7) Environmental pollution; (8) Other diseases. Lung cancer is the number one killer in malignant tumors. In the last thirty years, the mortality of lung cancer is the first one in all leading malignant tumors in the world; the incidence also is increasing. In 2000, DSEC noted that Macau population was 437 903 (47.3% male, 52.7% female), the mortality of lung cancer were 22.4/100 000 population (29.9/100 000 in male, 14.7/100 00 in female).

The aim of compilation the *Clinical Handbook of Lung Cancer* is concise, practical with Chinese-English bilingual for young doctors. They can use this handbook easily to understand new knowledge, early diagnosis and reasonable treatment, to improve the life quality and extend the survival period for patients with lung cancer.

By the end of twentieth century, tumor-related genes (e.g. tumor suppressor genes, antitumor genes) have been discovered, human being had grasped the outline of tumors. We believe that diagnosis and treatment of lung cancer and all malignant tumors will hopefully be captured and cured in twenty-first century.

Finally, I would like to thanks my teacher, Professor Emeritus Yoshihiro Hayata for the preface; to thanks supporter by Department of Health of Macau, and all domestic and macau contributors. I welcome any comments and criticisms regarding this handbook.



Huai-Shen WU, MD, FCCP

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1st September, 2001 Macau

作者序

在人類和癌症抗爭的歷史長河中，令人不安！癌症不像傳染病和愛滋病，可以用人類生活方式或行為去完全控制它；癌症常常無情和悄悄降臨，很少預警，難以根治。

二十世紀中，許多調查研究、實驗資料和生物現象都證明：癌症主要和人的老化、生活方式、精神心理、遺傳因素、民族性別、地理氣候、環境污染和其他疾病的八大因素相關。二十世紀癌症沒有被攻克，可見癌症發生發展的複雜性，用純醫學或單一因素去研究是遠遠不夠的。肺癌，可謂癌中之王。因為近三十年來，全球大多數國家和地區的肺癌死亡率一直居惡性腫瘤的第一位，發病率也在上升。澳門特區政府統計暨普查局公佈2000年9月1日，澳門人口437 903人(男47.3%、女52.7%)。2000年，澳門肺癌死亡率是22.4/10萬人口；男性、女性分別為29.9和14.7/10萬人口。

【肺癌臨床手冊】編寫的宗旨是“簡明扼要，切合實用，中英對照”，可讓全科醫生和中青年醫生對肺癌有更新的瞭解，達到臨床上早期診斷和合理治療，延長病人的壽命和保證生活質量。二十世紀末，由於致癌、抑癌基因的研究成功，科學家開始敢說，人類已經掌握了癌症之輪廓。相信在二十一世紀中，人類才能真正認識、徹底攻克包括肺癌在內的全部惡性腫瘤。

最後，我要衷心感謝我的導師、前國際肺癌學會會長、日本東京醫科大學前癌症研究所所長早田義博終身榮譽教授為本手冊賜賞序言，同時感謝國內著名肺癌專家教授們賜文，本書增色不少。還要衷心感謝澳門作者們的合作，以及澳門特別行政區社會文化司的支持和衛生局的資助。雖然編者們作了很大努力，但因水平有限，期盼同道和讀者的批評和指正。



吳懷申 謹識

2001年9月1日於澳門仁伯爵綜合醫院

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1. The New Concepts of Oncogenesis and Development of Lung Cancer

Dr. ZHOU Qing-Hua

Lung cancer, which was very rare at the beginning of the 20th century, is now the most frequent malignant tumor in the world. Consequently, lung cancer will remain a major cause of worldwide cancer death among both men and women in the 21st century. Despite advances in surgical and radiotherapeutic techniques and new chemotherapeutic agents, the 5-year survival of 15% has not improved significantly^[1]. It has been known that lung cancer is caused by exposure to carcinogens in tobacco smoke is unquestionable. About 85%~90% of lung cancer patients are smokers^[2]. Inherited predisposition may, however, be an important component in the oncogenesis and development of lung cancer, since fewer than 20% of smokers will develop lung cancer in their lifetime. Tremendous advances in the knowledge of lung cancer molecular biology have resulted in an appreciation of two new concepts critical to the carcinogenesis and progression of lung cancer: multistage carcinogenesis and field cancerization. In addition, each stage of the carcinogenesis and development of lung cancer is involved in lung cancer related-genes, which is also regulated by multigenes. Further understanding of these concepts should lead to identification of rational targets for preventive interventions and reversion therapy of lung cancer.

1.1 Multistage carcinogenesis of lung cancer

Carcinogenesis of lung cancer has become recognized as process involving an irreversible initiation phase, a reversible promotion phase, and finally an irreversible phase. Initiation is characterized by interaction of a carcinogen or procarcinogen with DNA to produce an irreversible alteration of cellular DNA. This initiation event may induce proliferation on the epithelial surface that may result in atypia. This atypia, in conjunction with a hyperproliferative epithelial lesion, may yield a recognizable precancerous lesion. This phase is characterized as promotion, and ongoing proliferation may occur. In a chronically proliferating

1. 肺癌發生發展的新概念

周清華

肺癌在20世紀初是罕見病，而目前是世界最常見的惡性腫瘤。21世紀肺癌將繼續是導致人類癌症死亡的首位。儘管外科治療和放射治療的進展和不斷有新的肺癌化療新藥出現，肺癌總的5年生存率仍未超過15%^[1]。目前已知絕大多數肺癌與吸煙有關，約85%～90%的肺癌患者是吸煙者^[2]。然而遺傳背景在肺癌的發生和發展中亦起重要作用。隨著肺癌分子生物學的進展，使人們逐漸認識到肺癌發生發展的兩個新概念，即肺癌發生發展的多階段學說和區域癌變學說。此外，人們亦逐漸認識到肺癌發生發展的每一個階段都是由一些肺癌相關基因調控的，而且是受多基因調控。對肺癌發生發展的多階段、多基因概念的進一步認識，將有助於肺癌的預防控制和逆轉治療。

1.1 肺癌發生的多階段學說

肺癌的發生發展過程大致可以被分為不可逆的激發，可逆轉的促進、進展和不可逆的侵襲，轉移等幾個階段。激發階段的特徵是致癌劑或前致癌物質與DNA相互作用導致細胞DNA產生一種不可逆性損害。這種激發作用可導致支氣管上皮細胞的增殖，並最終引起上皮細胞的非典型增生。上皮細胞的非典型增生，加上支氣管上皮細胞的過度增殖，被認為是一種支氣管上皮的癌前病變。這個階段被稱為支氣管肺癌的激發階段，並能進一步發展。支氣管上皮細胞的慢性過度增殖，在起動劑作用下能導致上皮細胞的惡性轉化，並最終形成具有臨床症狀的支氣管肺

epithelium, further action by a promoting agent can result in malignant transformation resulting in frank carcinoma. Promoters act to increase metabolic turnover and are marked by increased proliferation and cellular disorganization. Further progression results in the development of the capacity of the tumor to invade and metastasize. Characterization of this process has resulted in the understanding that while initiation is a rapid irreversible stage, promotion and progression involve multiple genetic events that occur over decades^[3].

1.1.1 Initiation

At present, it has been known that multiple agents were implicated in the process of carcinogenesis. Complete carcinogens are a class of compounds that are capable of both initiation and promotion. The early steps of carcinogenesis are characterized by multiple genetic events, including gene mutation, deletion, amplification, translocation, and mitotic recombination. These changes are associated with a clonal evolution of epithelial neoplastic transformation. Both oncogenes and tumor suppressor genes play an important role in the initiation process of lung cancer. Cellular oncogenes may arise as activated version of normal cellular growth-promoting agents, or protooncogenes. Activation may occur through changes in the structure of encoded proteins or deregulation of amount of such proteins. Some oncogenes and their protein products may disrupt steps in the pathways that may be response to mitogenic growth factors. As a result these pathways may be activated in the absence of normal growth factors. Genetic dysregulation can stimulate growth factor release exemplified by the activity of autocrine growth factors on tumor cells. Autocrine behavior is also demonstrated by constitutive activation of several growth factor genes by cells transformed by ras. Overexpression of these genes may cause ligand-independent receptor activation that leads to cell transformation and may contribute to the development of non-small cell lung cancer.

Tumor suppressor genes are believed to regulate proliferation in normal cells. Normal growth control is lost when these genes are inactivated. Several tumor suppressor genes have been linked to hereditary cancers. The first such discovery was in the hereditary retinoblastoma with an inherited deletion of the Rb gene on the long arm of chromosome 13. The Rb gene has also been found to be deleted in

癌。起動子能使上皮細胞代謝發生改變，並以細胞過度增殖和細胞結構排列紊亂為特徵。隨著病變的進一步進展，腫瘤細胞就具有侵襲和轉移的能力。目前已知肺癌發生發展的多階段學說的特徵是激發階段是一個快速、不可逆的階段，促進和進展則是一個需超過10年以上的漫長的發展過程，而且是受多基因參與調控的過程^[3]。

1.1.1 激發階段

目前已知在肺癌的激發階段，有許多因素參與肺癌的發生過程。完整致癌劑是一類在肺癌的啟動和發展過程中均起作用的物質。在肺癌癌變早期階段的特徵是多基因異常，包括基因突變、缺失、擴增、易位和染色體重排等。伴隨這些基因改變的是支氣管上皮細胞惡性轉化克隆的形成。癌基因和腫瘤抑制基因在肺癌的激發階段起重要作用。致癌物質可通過使正常細胞生長調節劑和原癌基因啟動，而使細胞癌基因活化。原癌基因可通過基因編碼蛋白結構改變或者蛋白量的缺失啟動。某些癌基因和蛋白產物還能破壞細胞有絲分裂生長因子的調節通路，其結果是這些信號通路在缺乏正常生長因子的情況下被啟動。細胞遺傳改變能通過肺癌細胞上生長因子自分泌通路的啟動，持續釋放生長因子，導致細胞無限止地生長。ras基因活化可以啟動細胞生長因子自分泌通路。功能異常的生長因子受體蛋白具有癌基因蛋白樣的作用，不斷向肺癌細胞釋放有絲分裂信號。癌基因的過度表達可使配體不依賴性細胞受體啟動，從而導致細胞轉化，並與非小細胞肺癌的發展有關^[4]。

腫瘤抑制基因具有調節正常細胞增殖的功能。當腫瘤抑制基因失活後，就失去對細胞增殖的控制。業已證明有許多腫瘤抑制基因與遺傳性腫瘤的發生有關。首先被發現的是13號染色體長臂上的Rb基因缺失與遺傳性視網膜母細胞瘤有關。在人小細胞肺癌中Rb基因有較高的缺失率。而在非小細胞肺癌中，約有50%的患