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Insights from the West

TCM in Metastatic Lung Cancer: Prognosis and Complementary Treatment of Advanced Pulmonary Non-Small-Cell Lung Cancer (NSCLC)

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ABSTRACT
Lung cancer is one of the most frequent and lethal cancers worldwide. The outcome depends on the extent of the disease (stage) and the physical condition of the patient ('performance status') at the time of diagnosis, the histological type, genetic mutations and treatment. The most frequent lung cancer type is non-small-cell lung cancer (NSCLC). Over the past three decades, the median survival time of advanced NSCLC has increased from approximately six months in the 1980s to nine months twenty years later, but mortality rates are still very high as most patients already have metastatic disease at diagnosis. This leaves radiotherapy, chemotherapy or targeted therapy as the therapeutic options for most patients. Targeted therapy (TT) can result in a median survival improvement of three to four months in subgroups with specific genetic mutations, but in non-Asians these mutations are rare. Consequently, in most NSCLC patients TT is not (yet) useful. A promising new development is nivolumab, a fully human IgG4 programmed death 1 (PD-1) immune-checkpoint–inhibitor antibody, which may restore antitumour immunity. Unfortunately, TT is very expensive and unaffordable for most patients in developing countries.

Understandably, many patients with metastatic NSCLC seek help with (much less expensive) traditional Chinese medicine (TCM) herbal treatment, which is patient-tailored based on specific TCM symptoms. However, although TCM herbal medication next to chemotherapy is widely used in China, until recently scientific proof according to conventional Western standards was scarce. First, we present three recent articles from two independent groups in China/Norway and in the USA which have given a strong positive signal that complementary/supportive TCM-herbal treatment next to conventional platinum-based chemotherapy, improves prognosis in advanced NSCLC patients. The set-up and the treatments in these studies show some differences. Yet, due to the comparable good survival rates, complementary TCM herbal therapy in metastatic NSCLC patients is an interesting complementary therapeutic consideration. This is especially interesting for nivolumab-treated patients, as several of the TCM herbs have an immune-stimulating effect. Then, more recently published evidence supporting the use of adjunctive TCM herbs combined with conventional treatment in lung cancer is presented. Finally, additional research needed in order to obtain definitive clinical evidence for the prognosis-improving effect of complementary TCM in combination with platinum-based chemotherapy in advanced lung cancer is briefly discussed, and recommendations are made for supportive clinical management of NSCLC with complementary TCM until such definitive data are available.

Epidemiology and survival of lung cancer
In the Western world, the incidence of cancers of the lung, colorectum, prostate, breast and endometrium has increased steadily, doubling over the past 50 years. In 2008, nearly 13 million new cancers were detected and many more patients continued to live with cancer.[1] In developing countries such as China, an even more impressive increase has been observed over the past two decades.[2-4] Today, primary lung carcinoma is the most frequent malignant tumour in the world (13% of all cancers, 18% of all cancer deaths).[5] In 2005, lung cancer in China was the leading cause of cancer deaths.[4]

Although the survival for certain malignant tumours has greatly improved since the 1970s, this is not true for lung cancer. In 1988, median survival time (MST) with inoperable NSCLC was 5-6 months following chemotherapy. Adding beta and gamma interferons resulted in 8 months survival,[5] but the 12-months survival of platinum-based chemotherapy compared with older chemotherapy regimens improved to 9 months MST and the 1-year survival by 5% only (34% vs 29%).[6-7] These data make clear that systemic therapies have not essentially improved survival in metastatic NSCLC in the Western world over the past 30 years and treatment badly needs to be improved.[8]

Understandably, many patients with metastatic NSCLC seek help with (much less expensive) traditional Chinese medicine (TCM) and other herbal treatments,[9] which is patient-tailored based on specific TCM symptoms. However, although TCM herbal medication next to chemotherapy is widely used in China,[10] until recently scientific proof according to conventional Western standards was scarce. Three recent articles from two independent groups in China/Norway and in the USA have given a strong positive signal that complementary TCM-herbal treatment next to conventional platinum-based chemotherapy, improves prognosis in advanced NSCLC patients.[11-13] These will be presented. Then, more recently published evidence supporting the use of adjunctive TCM herbs combined with conventional treatment in lung cancer will be described. Finally, additional research needed in order to obtain definitive clinical evidence for the prognosis-improving effect of complementary TCM in combination with platinum-based chemotherapy in advanced lung cancer will be briefly discussed, and recommendations are made for supportive clinical management of NSCLC with complementary TCM until such definitive data are available.

Factors increasing the risk of lung cancer
The International Agency for Research against Cancer (IARC) and the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) have published a comprehensive list of factors increasing and decreasing the risk of lung cancer (table 1).[14]

An epidemic of lung cancer, formerly a very rare disease, appeared in the 1940s and 1950s and was definitively identified as being caused by tobacco smoking by the ground-breaking epidemiologic work of Sir Richard Doll.[15-19] Although this finding has since been confirmed by a substantial body of work involving animal experiments, and cellular pathology, nevertheless the tobacco industry has managed to dispute this evidence and increase tobacco sales through successful lobbying and advertising campaigns.[20] Another major advance in the legal battle against tobacco, bans in public smoking established by California in 1998, was made possible by the first environmental chamber human clinical trial definitively finding that exhaled tobacco smoke is a toxin.[21] Today, it is generally accepted that smoking is by far the biggest cause of lung cancer, including a small proportion caused by exposure to second-hand smoke in non-smokers (passive smoking).[22]
The more smoked, the greater the likelihood of getting lung cancer, but the duration of smoking is even more important than how many cigarettes are smoked per day. Stopping smoking reduces the risk of lung cancer compared to continuing to smoke. The sooner one quits, the better. Cigarette smoking is the main cause of lung cancer, but pipe and cigar smokers are still much more likely to get lung cancer than non-smokers. However, sometimes lung cancer also occurs in non-smokers. This may be due to involuntary smoking, for example in restaurants. Not only is there a clear association between smoking and the incidence of lung cancer, but also between the duration of smoking and the mortality of lung cancer. The relation between smoking and lung cancer mortality therefore is in fact dose-dependent (figure 1).[23]

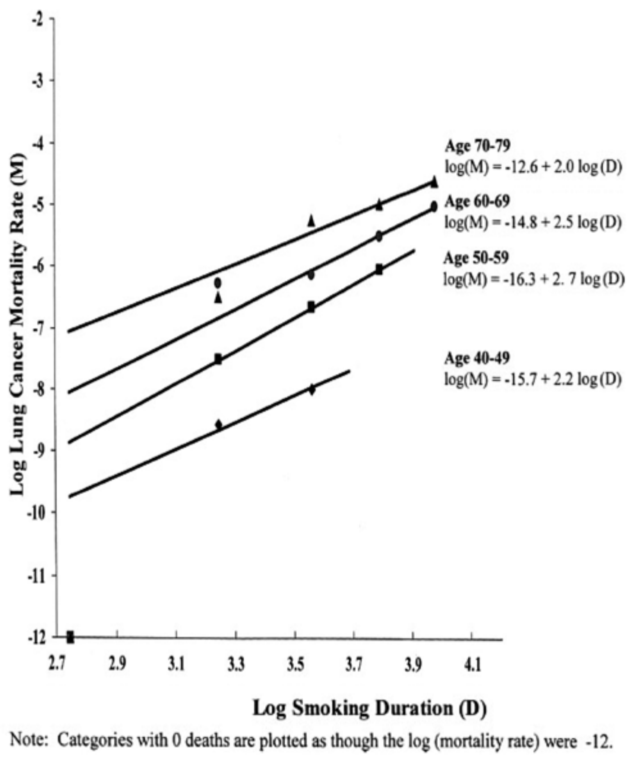


Figure 1. Relationship between lung cancer mortality and duration of smoking, the decades of adult lifespan.[23]

Recent findings show that in NSCLC adenocarcinomas, genetic mutations in the epidermal growth factor receptor (EGFR) occur more often in Asian than non-Asian descents and in non-smokers. As patients with adenocarcinomas are also more often females, it could be that oestrogen-dependent and other endocrine mechanisms play a role in the aetiology of these lung cancers.

Diagnosis, histological type
Patients with lung cancer present with a variety of symptoms, including shortness of breath, cough, pain, hoarseness, loss of voice and blood coughing. Pneumonia is the presenting feature in many patients. Paraneoplastic syndromes are frequent in lung cancer. A definitive diagnosis of lung cancer is made by radiological and pathological findings.[24] Figure 2 shows pathology specimens of lung cancer. There are different types of lung cancer according to the histological pattern. Two major subtypes are the non-small-cell lung cancers (NSCLC, 80% of all lung cancers) and small-cell lung cancers (SCLC, 20%), which have a different behaviour and sensitivity to treatment.[24, 25] NSCLCs are further divided according to their microscopy into squamous, adeno, and large-cell carcinoma (figure 3).

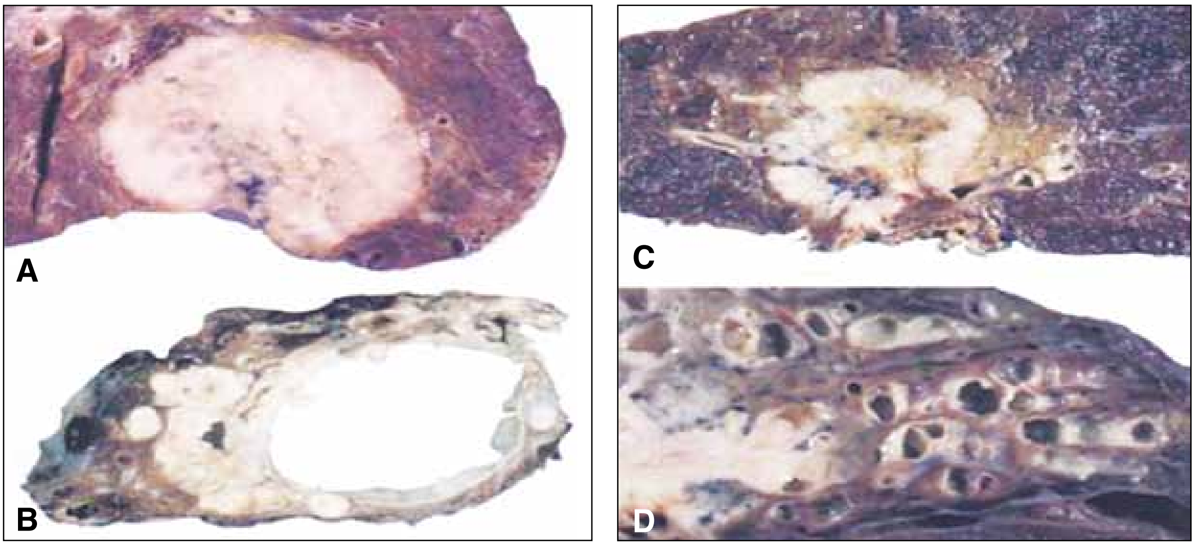


Figure 2. Examples of non-small-cell lung cancer. The whitish round nodule in the centre is the tumour. Note the dilated thrombi-filled blood vessels in D, in the right half of the image.

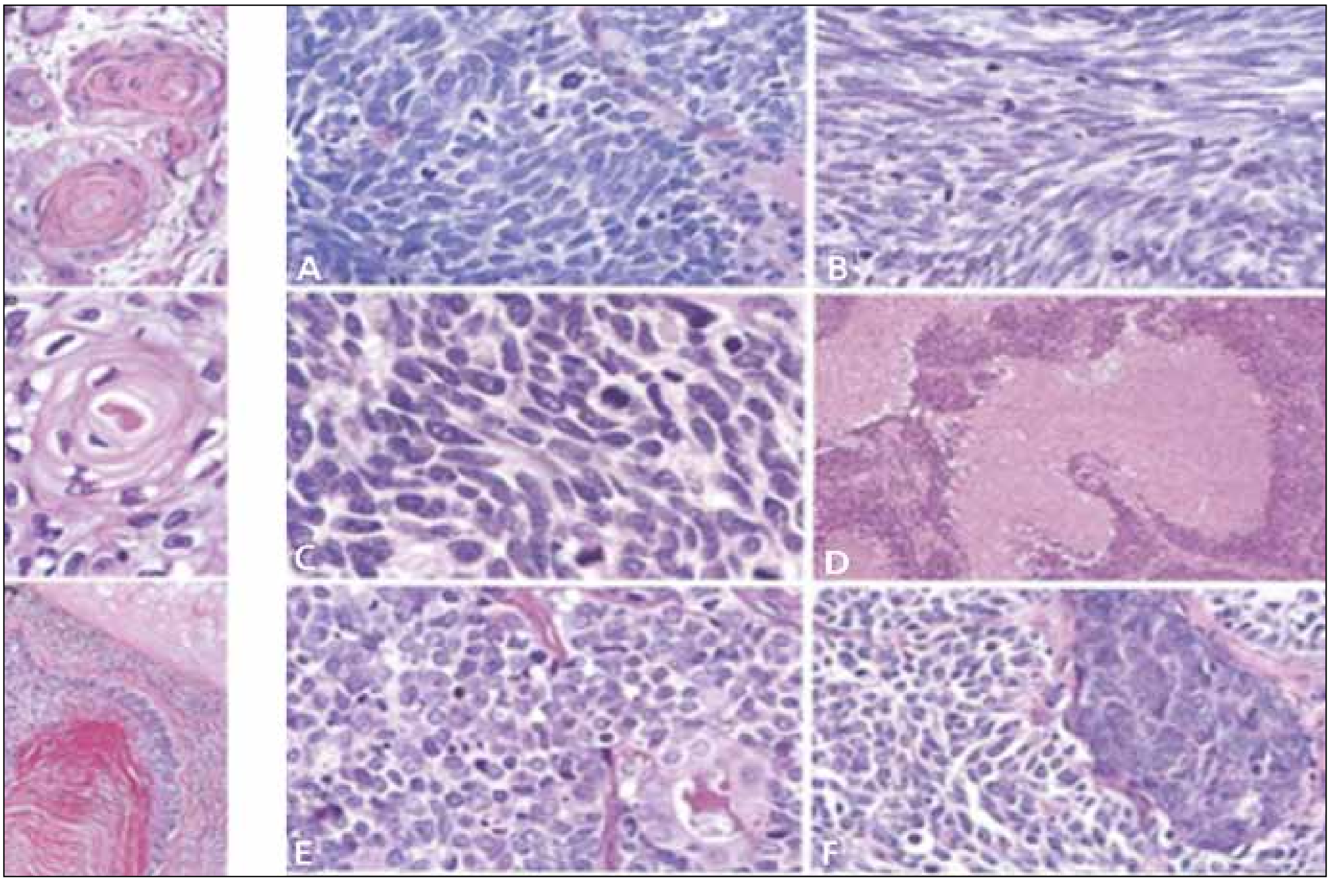


Figure 3. Left panel: Examples of squamous (left upper), large-cell (left middle) and adenocarcinoma (with central necrosis) (bottom). Right panel: Examples of small-cell cancer.

Stage (extent of disease) and prognosis

Next to the histological type, the stage (extent of the disease) is of the utmost importance for the prognosis and also determines treatment to a large extent. A rough staging procedure classifies the patients as having localised, regional, and distant disease. A more accurate staging system is the internationally accepted TNM staging method for NSCLC, in which tumour diameter (T), nodal metastases (N) and distant metastases (M) are taken into account (Table 1).[25] About one-third of patients with lung cancer are operable according to TNM stage, but the majority of patients present with inoperable stages 3 and 4 or advanced disease (i.e. tumour cells are found in the mediastinum, liver, adrenals, brain, skeleton or other organs). Sixty-five percent of the patients are inoperable at the time of diagnosis, a percentage very similar to other frequent cancers such as those from the colon and rectum. Operable patients are further subdivided as stage 1 and 2, with approximately 50% and 40% survival at 3 and 5 years.

Table 1. The TNM stage definition.

Tumour			
T1	<3 cm		
T2	>3 cm *or*		
	Involves main bronchus *or*		
	Invades pleura *or*		
	Atelectasis but not total lung		
T3	Any size involving chest wall, diaphragm, mediastinal pleura, parietal pericardium, main bronchus less than 2cm to carina but not carina		
T4	Any size involving mediastinum, heart, great vessels, trachea, oesophagus, vertebra, carina, separate tumours in same lobe, malignant pleural effusion		
Lymph nodes			
N0	No regional nodal metastases		
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension		
N2	Regional nodal metastases ipsilateral mediastinal and/or subcarinal lymph node(s)		
N3	Metas contralateral		
Metastases			
M0: No metastases			
M1: Distant metastases			
Stage grouping	**T**	**N**	**M**
Stage 1A	T1	N0	M0
Stage 1B	T2	N0	M0
Stage 2A	T1	T1	N1
Stage 2B	T2	N1	M0
	T3	N0	M0
Stage 3A	T1, T2	N2	M0
	T3	N1, N2	M0
Stage 3B	Any T	N3	M0
	T4	Any N	M0
Stage 4	Any T, T4	Any N	M1

Inoperable patients are divided as stage 3 and 4, with 10-15% and 1-2% 3- and 5-year survival. Inoperable lung cancer patients are usually treated with chemotherapy or radiotherapy. Small-cell lung cancers have a very poor prognosis (even worse than NSCLC), are staged as limited or extensive only and the prognostic effect of stage is much less impressive than in non-small-cell lung cancer patients.

Table 2 shows the numbers of patients per stage and the survival percentages.

Table 2. Incidence and survival of patients with lung cancer by stage.

			Survival (%)	
Stage	***Number of Patients***	***% of total***	***3-year***	***5-year***
Ia	687	13	71	61
Ib	1189	23	46	38
IIa	29	1	38	34
IIb	357	7	33	24
Stage 1 and 2	***2262***	***43***	***51***	***43***
IIIa	511	10	18	13
IIIb	1030	20	7	5
IV	1427	27	2	1
Stage 3 and 4	***2968***	***57***	***6***	***4***
Total	5230	10	26	21

Chemotherapy, targeted therapy, immunotherapy
It follows from the points discussed above that systemic chemotherapy remains the most often used treatment type in metastatic NSCLC in the Western world. These therapies are widely standardised and an extensive discussion is beyond the goal of this article.

The following platinum-based chemotherapy regimens are often used as first-line treatment in inoperable NSCLC patients: Cisplatin plus Gemcitabine, Cisplatin plus Vinorelbine, Cisplatin plus Paclitaxel, Cisplatin plus Docetaxel or Carboplatin plus

Paclitaxel. The dosages are described elsewhere.[26, 27] Targeted therapy has been discussed above. Radiotherapy is usually not given routinely but as indicated by the individual clinical and radiologic findings.

Genetics and targeted therapy

In 2000, President Clinton of the United States of America declared the Human Genome Project completed. The hopes for a soon to be explosion of breakthrough medicines were high, as the prime minister of the United Kingdom at that time also expressed in a speech for the British parliament: "This will be a breakthrough exceeding the discovery of antibiotics." Indeed, the theoretical possibilities are enormous. Celebrating his honorary doctorate from the University of Antwerp and appointment as long-term visiting professor at Harvard medical school, the first author of this article stated in the summer of 2000 in an interview published in many Dutch newspapers: "It is expected that within one decade, intelligent cocktails of new drugs, developed on the basis of molecular studies, will greatly improve the prognosis of patients with metastatic cancers." However, what has actually been discovered, what has changed in the insights into the diagnosis and treatment of lung cancer, and the prognosis of patients with metastatic lung cancer since these optimistic views were aired nearly 15 years ago? The following section will therefore pay special attention to genetics and targeted therapy in NSCLC.

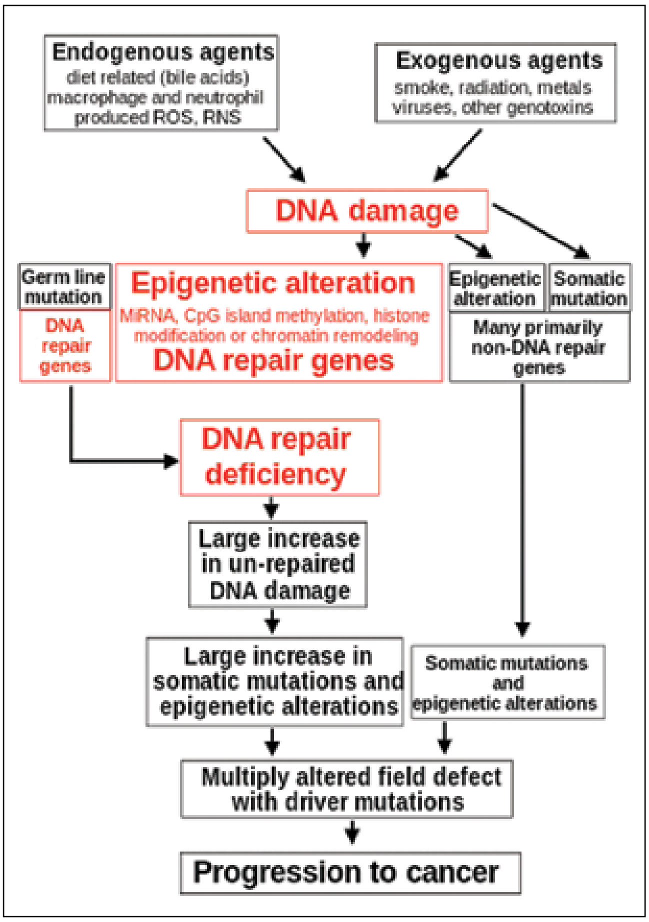


Figure 4. Genetic and epigenetic factors involved in the development of cancer.

Lung cancers show considerable genetic diversity, but genetic changes are frequent in all major histologic subtypes, such as loss of heterozygosity (LOH) at many different loci, including chromosomes 3p14-23, 8q21-23, 9p21, 13q, 17q, 18q and 22p. Three frequent chromosomal aberrations emerge as common, such as TP53, retinoblastoma pathway related and LOH at 3p. This has led to the following genetic models for the development of non-small-cell lung cancer (figure 4).[28] However, the classical histological distinction into non-small-cell and small-cell lung cancer has not changed.

An area of special interest since 2000 has been targeted therapies (TT). Indeed, certain mutation patterns in NSCLC (especially in adenocarcinomas) have emerged with therapeutic impact, in epidermal growth factor receptor (EGFR), KRAS, and anaplastic lymphoma kinase (ALK). Such mutations can influence response to targeted therapy.[29-31] EGFR is a cell surface protein for the growth factor EGF and EGFR mutations are seen more frequently in non-smokers and much more frequently in Asian than in non-Asian descents (50% versus 10%).[32] However, prospective population-based testing in Norway showed a much lower mutation rate than 10% (unpublished results, 2014). KRAS mutations are associated to EGFR-TKIs resistance.[33,34] Fusion between echinoderm microtubule-associated protein-like 4 (EML4) and ALK is seen in 2-7% of NSCLC adenocarcinomas and EGFR and ALK mutations are mutually exclusive. Consequently, ALK rearrangements are not likely to respond favourably to EGFR-targeting TKIs but rather on ALK inhibitors.[34-36]

Gefitinib (Iressa®) was the first EGFR-TKI evaluated in a phase III trial and approximately 10% of patients responded to the therapy but without survival benefit[37] and it has been withdrawn in the United States. Other clinical trials found improved progression-free-survival with erlotinib (Tarceva®) in patients with EGFR mutations.[38, 39] Comparison of the TKI Afatinib (Gilotrif) to pemetrexed/cisplatin chemotherapy showed 11 months progression-free survival (PFS) in the afatinib group versus 7 months in pemetrexed/cisplatin.[40] However, the survival of the chemotherapy-only group was very poor.

Prospective trials demonstrating the value of testing for KRAS mutations and to tailor therapy are so far lacking. Meta-analyses found a trend that KRAS mutations are associated with a lowered response to EGFR-TKIs, but it is unclear whether mutation status predicts reduced progression-free or overall survival.[41]

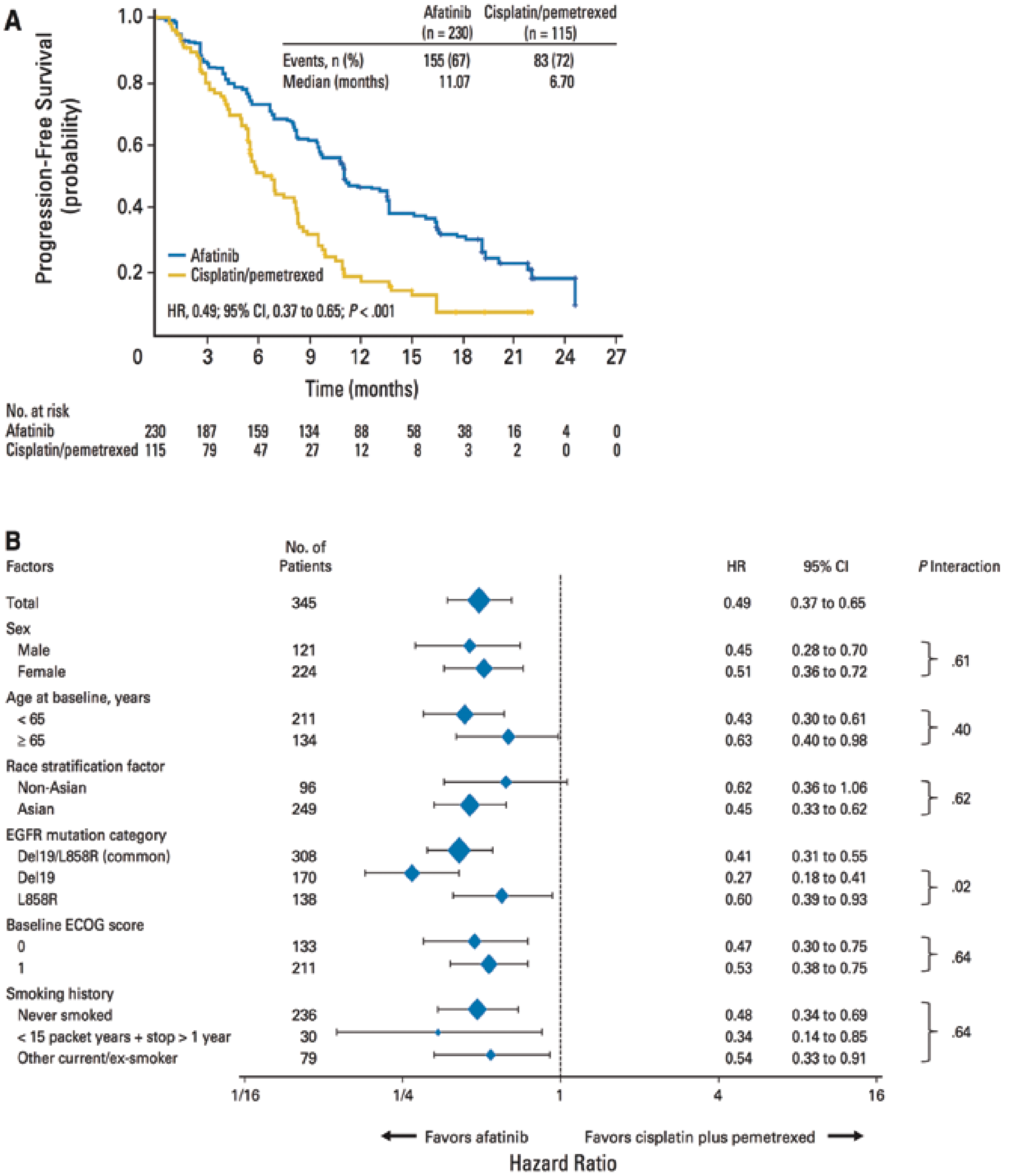


Figure 5. Comparison of patients with advanced non-small-cell lung cancer treated with either afatinib (Gilotrif) or pemetrexed/cisplatin chemotherapy (Sequist, L. V. et al. (2013). *JCO*; 31:3327-34). Note the survival advantage of afatinib-treated patients. However, the survival of pemetrexed/cisplatin treated patients is considerably worse than usually described. This could give a too positive impression of the effect of afatinib.

Patients with the EML4-ALK fusion, nearly all of whom had progressed despite at least one prior line of therapy, showed response rates of approximately 50% to 60% with crizotinib. Response duration was 42-48 weeks.[35, 36] As phase III trials are still underway and survival data are not yet available, a retrospective, nonrandomised analysis was undertaken.[41, 42] In crizotinib as second-line therapy, the 1- and 2-year overall survival rates were 70% and 55%. By contrast, ALK-positive matched controls had a 1-year survival of 44% and a 2-year survival of 12%, whereas ALK-negative controls had a 1-year survival of 47% and a 2-year survival of 32%.

A very recent new development is the following. Patients with advanced squamous-cell NSCLC who have disease progression during or after first-line chemotherapy have limited treatment options. In a randomised, open-label, international phase 3 study, the efficacy of nivolumab, a fully human IgG4 programmed death 1 (PD-1) immune-checkpoint-inhibitor antibody, as compared with docetaxel was evaluated. Overall survival response rate and progression-free survival were significantly better with nivolumab than with docetaxel, regardless of PD-L1 expression level.[43] Similar results were obtained for non-squamous metastatic lung cancer.[44] Unfortunately the costs of treatment are very high.

Apart from the latter results, most positive results for targeted therapy are relevant to relatively small subgroups in the Western world. Therefore, nearly 15 years after the expectations and promises in 2000 about the diagnostic and therapeutic impact of genetic medicine, we must conclude that the high hopes have not yet been realised, and certainly not for many patients with metastatic lung cancer. Apparently, the technical difficulties are much greater than expected. In agreement with this conclusion, in January 2015, AstraZeneca, one of the large pharmaceutical companies in the world, announced research collaborations aimed at harnessing a pioneering genome-editing technique and expects to identify and validate new drug targets in preclinical models that closely resemble human disease.

Proof for the effect of TCM herbal treatment in lung cancer

Herbal therapy is widely used for lung cancer in China and other East-Asian countries. Also outside these countries, complementary and alternative (i.e. scientifically unproven) medicines are used by up to 48% of lung cancer patients, but have seen little formal assessment of survival efficacy. Clinical experience from TCM suggests that complementary herbal treatment improves prognosis and quality of life. In 1996, Liu et al described a prospective randomised clinical trial on 304 patients with stage IIIb and IV adenocarcinomas of the lung.[45] They showed that TCM herbal treatment alone was more effective than using conventional chemotherapy of that time. The 1-year survival rates were 61% versus 37% ($P<0.01$), median survival times of 13.7 and 8.7 months ($P<0.01$) and 5-year survival rates 24% and 0% ($P<0.01$). However, target treatment was still unknown when the latter study was performed and, as mentioned, chemotherapy has also become slightly more effective since then. We can thus say that scientific proof according to conventional Western standards for using TCM herbs in lung cancer is scarce.

TCM, TCM-syndrome differentiation and principles of TCM herbal treatment

Traditional Chinese medicine (TCM) is a very old holistic medical system for diagnosis, prevention and treatment of diseases and has been an integral part of Asian cultures for thousands of years.[46] TCM uses experience-based therapies such as acupuncture and herbal medicine and is characterised by its underpinning theoretical guide, i.e. the philosophy of *yin-yang* balance.[47-51]

The first known scientific and systematic review of TCM is about 2,000 years old. Since then, a continuous development has taken place. In the first half of the 20th century, TCM was in decline in China, but since the 1950s, it has seen an impressive revival with an estimated 350 million TCM treatments given nationwide in 2008. In the USA, after 25 years intensive studies, in 1997 the Food and Drug Administration approved acupuncture as a medical technique. Since then, the number of TCM practitioners has greatly increased. The United States National Institute of Health has funded major basic and translational research into TCM herbs and acupuncture. The same holds for China. For example, the Shanghai Institute of Materia Medica has over 500 PhDs working with the most advanced scientific research methods and regular publications in top international journals. Rumours are that several pharmaceutical companies have heavily invested in the development of new drugs from ancient TCM herbs. A forthcoming publication in *Seminars in Cancer Biology* (November 18, 2015) with 180 named co-authors advocates moving to TCM as a supplement/alternative to targeted therapy. It is based on combining phytochemicals, extracts or low-toxicity drugs with activity against known hallmarks of cancer, in order to multi-target cells that are resistant to targeted therapies (Gyllenhaal, C., personal communication 2015, see www.gettingtoknowcancer.org).

TCM herbs are given based on the TCM syndrome differentiation diagnosed by a TCM medical specialist. Patients with the same disease (i.e. Stage IV adeno-carcinoma of the lung) may have different TCM syndromes. The TCM herbs are adjusted to the individual patient's TCM syndromes and this is widely regarded amongst TCM specialists in China to determine the efficacy of the treatment and thereby the prognosis.

TCM syndrome differentiation is general knowledge and described in many textbooks. The following therefore is only a general outline of the TCM syndrome differentiation used and the herbal treatment given to patients.

In the Longhua University Hospital of the Shanghai University of Traditional Chinese Medicine, which largely dictates TCM treatment strategy in Shanghai (a city with 24 million inhabitants), the TCM syndromes described below are used. Zheng, et al catalogued details of the different TCM terms such as *qi* and *yin*, and the TCM syndrome differentiation methods used in diagnosis.[52]

The syndromes can be diagnosed if any two of the main symptoms with any two of the secondary symptoms are present (see below). The herbal treatment is adapted to the syndromes.[53]

1. *Syndrome of Deficiency of both Qi and Yin*
Main symptoms are: cough, little phlegm, low spirit, weakness, spontaneous sweating or night sweating, red or pink tongue, or teeth-marks at the margins of the tongue, thin tongue coating, and thready, weak pulse. Secondary symptoms are: phlegm with blood, faint low voice or cough, dry mouth and little desire to drink. The treatment principle is strengthening *qi* and nourishing *yin*.

Commonly used herbs are: Radix Astragali seu Hedysari, Rhizoma Atractylodis Macrocephalae, Radix Glehniae, Radix Asparagi, Radix Ophiopogonis, Semen Armeniacae Amarum.

2. *Syndrome of Deficiency of Yin and Internal Heat*
Main symptoms are: cough, no phlegm, low fever, night sweating, red tongue, eroded fur or mirror-like tongue, and thready, rapid pulse. Secondary symptoms are: phlegm with blood, chest pain, shortness of breath, dry mouth, and insomnia. The treatment principle is nourishing *yin* and clearing Lung-Heat.

Frequently used herbs are: Radix Glehniae, Radix Asparagi, Radix Ophiopogonis, Bulbus Lilii, Semen Armeniacae Amarum.

3. *Syndrome of Deficiency of Qi*
Main symptoms are: cough, phlegm, low spirit, weakness, pale and plump tongue or tongue-margin teeth-marks, white greasy fur on the tongue, and soft moderate or soft slippery pulse. Secondary symptoms are: shortness of breath, pale complexion, anorexia and loose stool. The treatment principle is strengthening *qi*.

Typical herbs used are Radix Pseudostellariae, Rhizoma Atractylodis Macrocephalae, Poria, Pericarpium Citri Reticulatae and Rhizoma Pinelliae, while some other herbs are flexibly changed according to the symptoms.

4. *Syndrome of Deficiency of both Yin and Yang*
Main symptoms are: cough, shortness of breath, severe dyspnea after movement, frequent nocturnal urination, aversion to cold and cold limbs, pink tongue, thin tongue coating, deep and thready pulse. Secondary symptoms are: severe dyspnea, soreness and weakness of waist and knees, tinnitus, low spirit, weakness. The treatment principle is strengthening *yin* and warm Kidney.

Frequently used herbs are Radix Glehniae, Radix Asparagi, Radix Ophiopogonis, Herba Epimedii (Epimedium herb), Semen Cuscutae (dodder seed).

The TCM herbs used for the different treatments mentioned above are adapted to the TCM syndromes which can vary over time in the same patient. For details of some of the herbs, see [54-63].

Side effects of these TCM herbs are minimal and consist of mild temporary abdominal distension, nausea and sometimes diarrhoea. Rarely, (usually) transient and very mild liver and kidney damage can occur. For this reason, we perform standard liver and kidney tests at the start of herbal treatment, and with long-term treatment at regular intervals.

Is TCM used in Western Hospitals?
In China, traditional Chinese medicine is widely used in TCM hospitals, but Western medicine hospitals in China often also have large TCM outpatient clinics and departments. For example, one of the top cancer centres in China, the Fudan University Shanghai Cancer Centre, has two floors with 140 beds for hospital in-patients, a very busy out-patient TCM service and more than 50% of the pharmacy department is for TCM medical herbs.

What is the situation in the Western world? Is TCM a matter of Chinatown areas, or shabby back-street shops driven by persons with dollar signs in their eyes? There is no doubt that such practices exist. However, over the past decade a strongly increased interest in TCM and complementary medicine has occurred in the Western world. This is in part driven by the fact that many Chinese who have emigrated to the USA, Canada, Australia and the EU, are used to and trust TCM. However, also non-Asian inhabitants are increasingly interested.

As far as is known, in Norway or the Netherlands herbal medication is not given in hospitals, although acupuncture is more widely used, and in certain hospitals in Norway and the Netherlands, mostly for pain treatment and during delivey. However, also top quality hospitals in the USA such as MD Anderson Cancer Center (Houston, Texas), the Sloan Kettering Memorial Cancer Center in New York and the Johns Hopkins Hospital in Baltimore have extensive integrated medicine/ integrated oncology departments with large clinical treatment and research programmes.

http://www.mskcc.org/cancer-care/integrative-medicine,

http://www.hopkinsmedicine.org/integrative_medicine_digestive_center/

http://www.mdanderson.org/education-and-research/departments-programs-and-labs/programs-centers-institutes/integrative-medicine-program/index.html

We thus can say that TCM is widely used in some of the world's highest ranking hospitals.

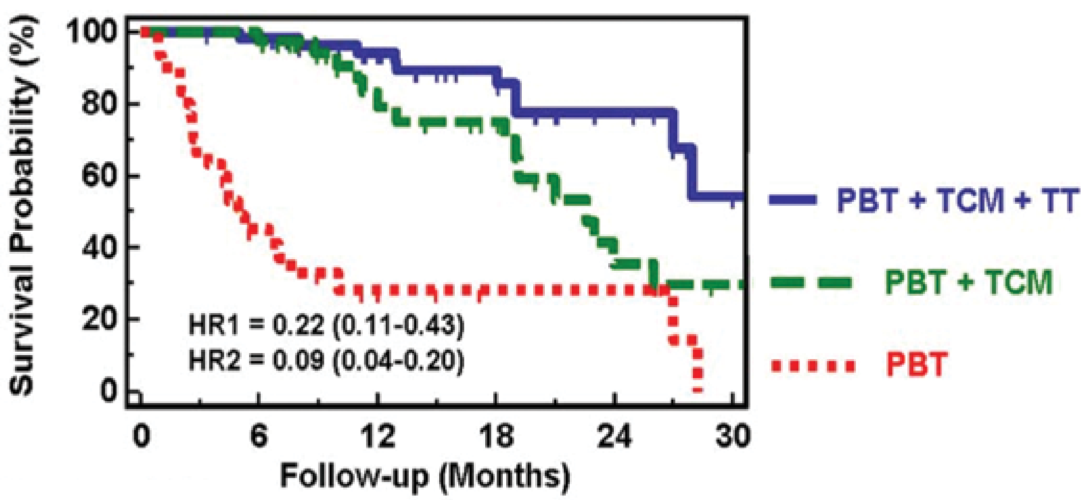
Recent proof for the favourable effect of complementary TCM herbs next to conventional treatment in lung cancer

Understandably, many patients with metastatic NSCLC seek help with traditional Chinese medicine (TCM) herbal treatment. Although TCM herbal medication next to chemotherapy is widely used in China, until recently scientific proof according to conventional Western standards was scarce. Two recent independent studies have changed this. These will be briefly described.

‘ TCM herbal treatment may improve survival of stage IV pulmonary adenocarcinoma patients treated with platinum-based chemotherapy without or with targeted therapy ’

Guo et al, Shanghai

In a retrospective case-control study from Shanghai, China, 133 fully ambulant out-patient clinic patients with primary stage IV pulmonary adenocarcinoma were analysed. They were all treated with platinum-based chemotherapy alone or PBT with/without second-line targeted therapy, with/without complementary TCM. The question was whether TCM herbs improve survival.



Number at risk

PBT + TCM + TT	62	60	39	26	11	2
PBT + TCM	41	39	20	16	6	1
PBT	30	11	5	2	2	0

Figure 6. Survival curves and patients at risk for the 3 different groups of patients (PCB = platinum based therapy; TCM = traditional Chinese herbal medicine; TT = targeted therapy). Note the much better survival of the TCM and TT treated patients.

Univariate (Kaplan-Meier) and multivariable (Cox model) survival analysis were performed, using disease-specific mortality as an endpoint. Gender (P=0.002), targeted therapy (P<0.0001) and TCM herbal treatment (P<0.0001) had univariate prognostic value but not age, radiotherapy or TCM syndrome differentiation (P>0.10). TCM herbal treatment (P<0.0001) and targeted therapy (P=0.03) had multivariable independent prognostic value. A total of 103 patients were treated with TCM, of which 62 received PBT, TT and TCM; 41 received PBT, TCM but no TT. The 1-year overall survival rate of the 103 patients was 88%, with median survival time (MST) of 27 months, contrasting 27% 1-year overall survival and MST of 5.0 months for non-TCM treated (n=30) patients. Patients with combined chemotherapy, targeted therapy and TCM (n=62), TCM without targeted therapy (n=41), or chemotherapy only (n=30), had 12 months survival rates of 94%, 78% and 27% respectively; for these 3 groups, MST was not reached (mean survival time of 30.9 months), 22.6 and 5.0 months respectively (P < 0.0001) (figure 6).

‘ The median survivals of the original PBT patients and the PBT+TCM treated patients were 5.0 and 22.6 months, a difference of nearly 18 months. The 1-year survivals were 27% and 78% ’

Guo et al concluded that TCM herbal treatment may improve survival of stage IV pulmonary adenocarcinoma patients treated with platinum-based chemotherapy without or with targeted therapy. This warrants formal phase 1, 2 and 3 trials and ultimately properly designed prospective clinical validation trials with adequate methodology developed for data collection.

McCulloch et al, San Anselmo, California, USA

The second article was published by McCulloch et al. from the Bay-Area Chinese medicine centre (Pine Street Foundation), San Anselmo, California, USA, in collaboration with investigators at the University of California Berkeley, Kaiser Permanente Division of Research and the Chinese Academy of Sciences.[11] They investigated in a 10-year retrospective study the effect of Pan-Asian medicine + vitamins (PAM+V) therapy on survival in a consecutive case series of all non-small-cell lung cancer patients (n=239) presenting at their clinic. They compared short-term treatment lasting the duration of chemotherapy/radiotherapy, to long-term continuing beyond conventional therapy. They also compared PAM+V combined with conventional therapy to conventional alone, using concurrent controls from Kaiser Permanente and California Cancer Registry, with adjustment for confounding. Survival was analysed with Kaplan-Meier, Cox regression and newer methods for causal inference: propensity score and marginal structural models (MSM); they reduce bias in non-randomised studies, making treatment groups comparable based on their probability of having been treated, with results comparable to randomised trials. Randomised trials are desirable to less than 5% of cancer patients.

‘ PAM+V combined with conventional therapy improved survival, compared to conventional chemotherapy alone ’

They found that long-term use of PAM+V beyond completion of chemotherapy reduced risk of death in stage IIIB by 83% (HR=0.17; 95% CI 0.08, 0.36) and stage IV by 72% (HR=0.28; 95% CI 0.12, 0.61), compared to short-term use only for the duration of chemotherapy. Long-term use of PAM+V combined with conventional therapy reduced risk of death in stage IIIA by 46% (HR=0.54; 95% CI 0.41, 0.70), stage IIIB by 62% (HR=0.38; 95% CI 0.28, 0.50), and stage IV by 69% (HR=0.31; 95% CI 0.20, 0.48), vs. conventional alone. They concluded that long-term PAM+V showed better survival, versus short-term lasting only the duration of conventional therapy. PAM+V combined with conventional therapy improved survival, compared to conventional alone.

‘ Long-term PAM+V showed better survival, versus short-term lasting only the duration of conventional therapy ’

PAM+V combined with conventional therapy improved survival, compared to conventional therapy alone. Figure 7 graphically illustrates the survival at 1-year follow-up in the studies from China and the USA. Note the similarity in survival rates, and the remarkable prognostic advantage of patients who received complementary herbal treatment.

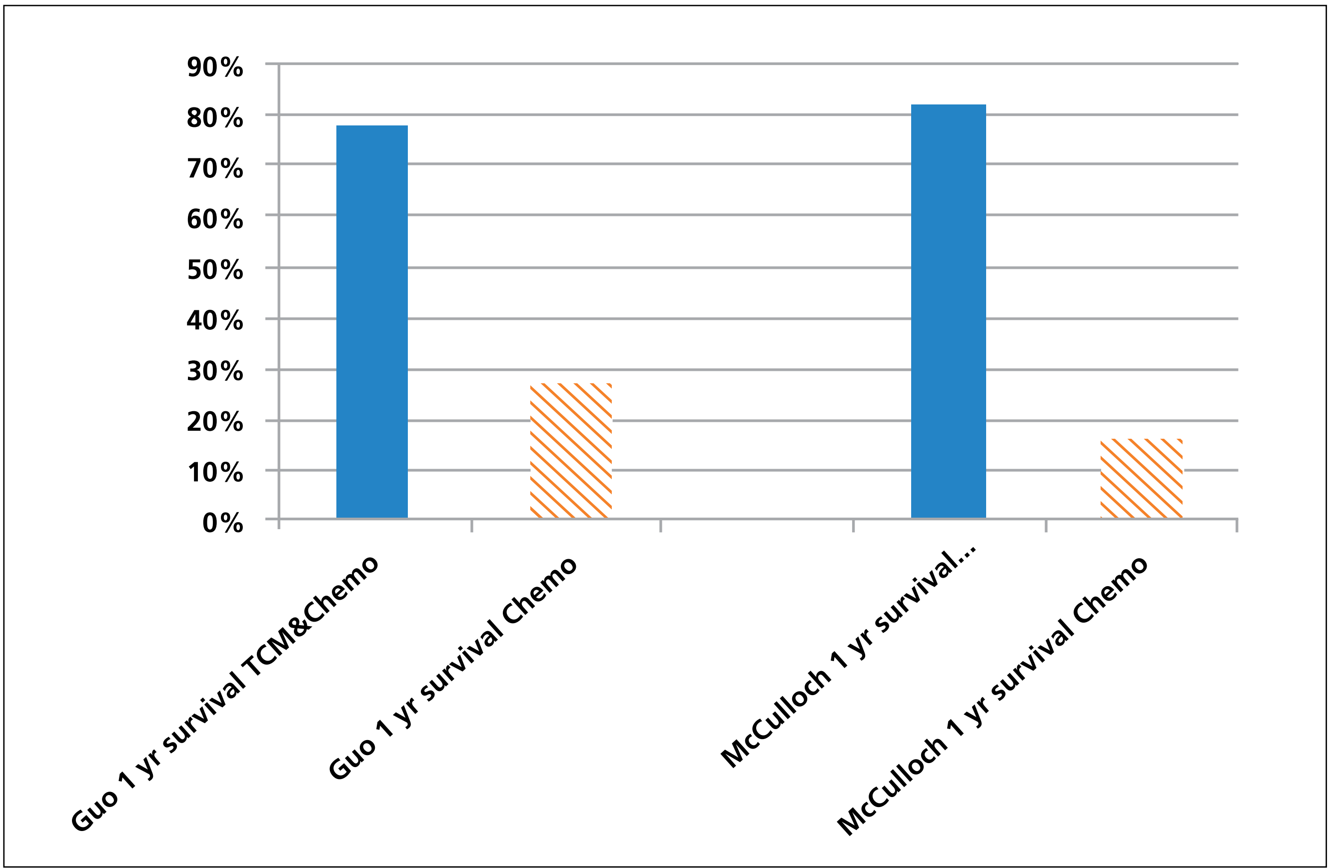


Figure 7. One-year survival rates in the studies from China (left) and the USA (right), with conventional chemotherapy alone (hatched red bars) and combined chemotherapy and herbal medication (blue bars).

Is lag time to treatment important for prognosis?
In spite of these positive results, it should be remembered that patients often get the diagnosis of metastatic cancer in different hospitals from where they receive TCM herbal treatment, and even within the same hospital, the TCM doctors may have a (short) waiting list. Moreover, patients also may need time to decide whether they will use TCM herbal treatment. The consequence is that there is a certain lag time to TCM herbal treatment from 1 week, up to several months for certain famous TCM specialists.

An extended lag time to treatment of patients with an overall very poor prognosis may improve the prognosis of the remaining patients, as patients with the worst prognosis already may have died before they have ever been seen by the TCM specialists or started TCM treatment. Patients with the same stage and histologic type of disease seen by TCM specialists therefore may have better survival expectancy than the group of all (consecutive) patients. It is therefore possible that the improved survival of stage IV pulmonary adenocarcinoma patients treated with PBT+TCM versus PBT alone, is due to lag time to treatment bias which is the combination of the waiting time to see a doctor, or 'doctor's delay', and the delay due to the patients' decisions to seek TCM treatment. However, it is unknown how strong the influence of this phenomenon is, if there is any influence at all. We have therefore performed a computer simulation exploring the effect of an artificial lag time on the survival of PAC patients with PBT treatment.[13] The median and 1-year survival of patients with an artificial lag time to treatment of up to 5 months have been studied. We also compared these survivals with a group of PBT patients treated with additional TCM treatment, with little or 1-2 months lag time to treatment. The median lag-time-to-treatment was 3 months. In the first 3 months, about 35% of the patients die, but hereafter the survival curve flattens off and the death of the next 35%-40% of patients takes 9 months. Leaving out patients up to 3 months therefore would be a reasonable choice. To be on the safe side, we investigated the effect of leaving out patients up to 4 months. Kaplan-Meier survival curves were used.

It is clear from figure 6 that the median survivals of the original platinum-based chemotherapy and the platinum+TCM treated patients were 5.0 and 22.6 months, a difference of nearly 18 months. The 1-year survivals were 27% and 78%. The different panels in figure 8 show the survival curves of the patients with PBT, and with increasing lag times to treatment (simulated by leaving out from the PBT treated patients those with follow-up of less than 1, less than 2, less than 3 and less than 4 months). Table 3 shows the median and 12-month survival of each group.

Note that up to 2 months lag time to treatment bias, there is hardly any effect on the median and 1-year survival, and the differences are not significant. Only after 3 months lag time, the difference becomes (just) significantly different from the original total group of PBT-treated patients, but improved survival becomes only clinically impressive after 4 months lag time to treatment. However, even then, the PBT+TCM group still has significantly better survival (P=0.01, hazard ratio=0.50 for up to 4 months lag time to treatment) (Table 1, right column). Moreover, there is no survival difference between general TCM specialists (with little lag time to treatment) and a famous TCM specialist (with more lag time to treatment) (P=0.79, figure 9).

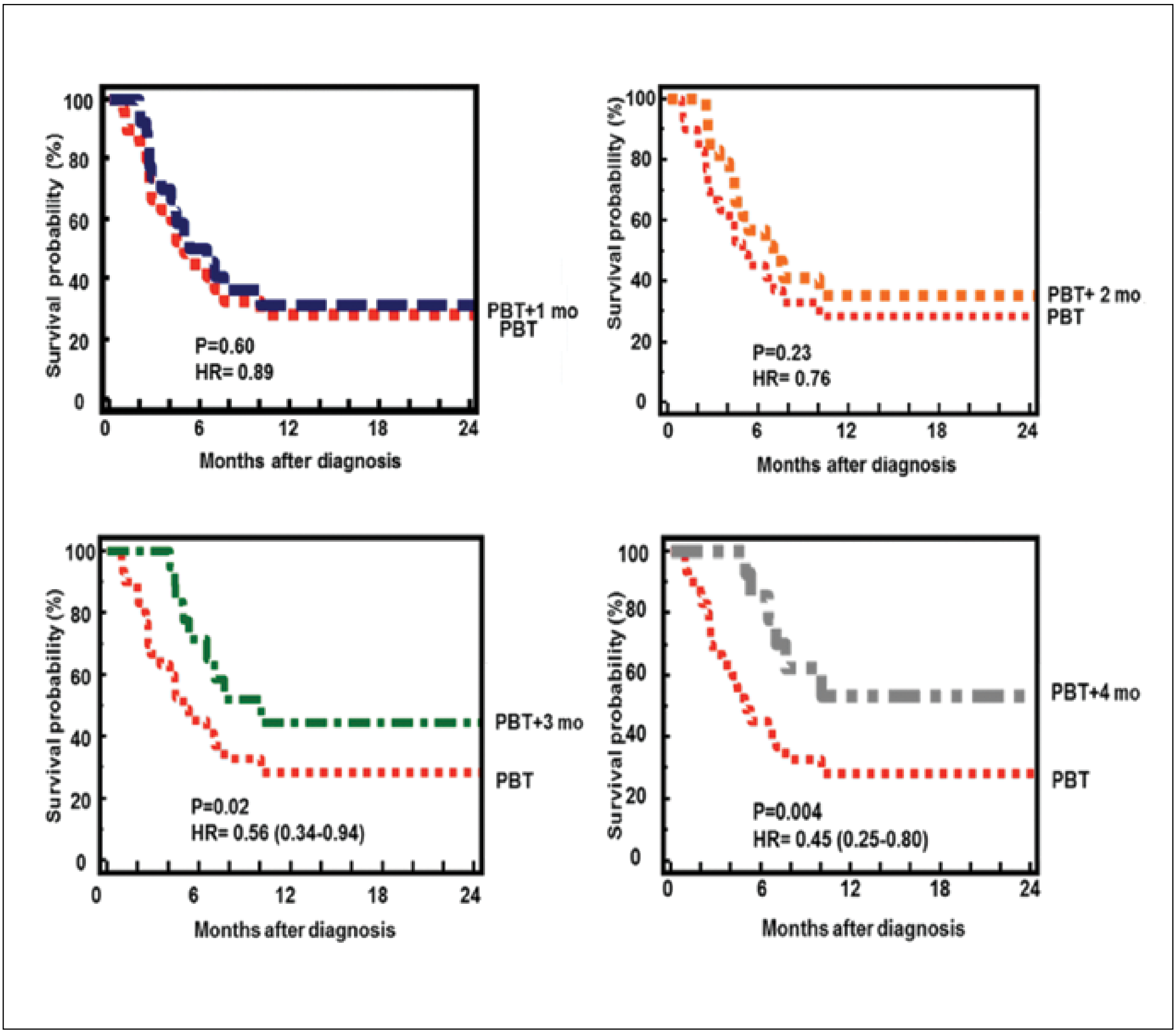


Figure 8. Panels a, b, c and d show the survival curves of the patients with platinum-based chemotherapy (PBT), and with increasing lag times to treatment (simulated by leaving out from the PBT treated patients those with less than 1, less than 2, less than 3 and less than 4 months follow-up).

Table 3. The influence of lag time to treatment in platinum-based treated stage IV pulmonary adenocarcinomas on median and 1-year survival, the probabilities of no difference with the original platinum-based treatment (PBT) patients without lag time to treatment and the survival of PBT plus treatment with traditional Chinese medicine herbs (TCM).

Group	Median survival (months)	1-year survival (%)	Probability of no difference with PBT	Probability of difference with PBT+TCM
PBT, all patients	5.0	27%	Not applicable	P<0.00001 HR=0.22 (0.11-0.43)
PBT, 0-1 months follow-up left out	5.5	32%	P=0.60 HR= 0.89	P < 0.0001 HR=0.26 (0.16-0.42)
PBT, <2 months follow-up left out	6.5	36%	P=0.23 HR= 0.76	P < 0.0001 HR=0.29 (0.18-0.48)
PBT, <3 months follow-up left out	9.0	43%	P=0.02 HR= 0.56 (0.34-0.94)	P<0.0001 HR=0.39 (0.22-0.68)
PBT, <4 months follow-up left out	18.3	52%	P=0.004 HR= 0.45 (0.25-0.80)	P=0.03 HR=0.50 (0.27-0.94)
PBT+TCM, all follow-up	22.6	78%	P<0.00001 0.22 (0.11-0.43)	Not applicable

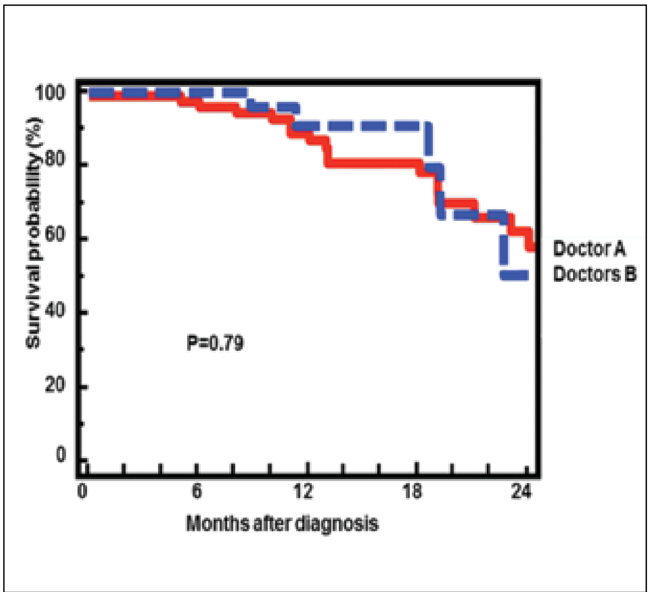


Figure 9. Comparison of patients with PBT+TCM, treated by a famous TCM specialist with more lag time to treatment ('doctor A', continuous line) and different general TCM specialists with little lag time to treatment ('doctors B', interrupted line). There is no difference in the survival results (P=0.79).

With up to 4 months lag time to treatment due to combined patients' and TCM doctor's waiting time, the improved survival of PBT+TCM performance score 0-1 (fully ambulant) patients at the time of diagnosis still is significant (P<0.01, hazard ratio 0.51). Moreover, the survival of patients treated by TCM doctors with little or more months lag time to treatment, was not different (P=0.79) (figure 9). It is concluded that increasing lag time to treatment with up to 4 months improves the median and 1-year survival of PBT patients without TCM but is unlikely to explain the greatly improved prognosis of PBT+TCM treated patients with fully ambulant stage IV pulmonary adenocarcinoma.

Overall comments

The two studies from China and the USA differ in their design, enrolment period, chemotherapies and herbs given, lack of target therapy in McCulloch's study and a number of other details. In spite of this it is striking that the survival rates due to additional TCM herbal medicine in Guo's study and PAM+V in McCulloch's study, compared to chemotherapy, are of the same order of size (78% and 82%, Figure 7). The somewhat worse prognosis in McCulloch's chemotherapy-only patients compared with Guo's patients, could be either due to more effective chemotherapy in 2007-09 than in 1988-93, or caused by the fact that Guo studied adenocarcinomas only and McCulloch all histologic subtypes of non-small-cell lung cancers. It is therefore concluded that the studies give a strong positive signal that TCM-herbal treatment next to conventional platinum-based chemotherapy, may improve prognosis in advanced non-small-cell lung cancer patients. Therefore, adjuvant TCM herbal therapy in metastatic lung cancer patients is an interesting therapeutic research topic.

‘ The studies give a strong positive signal that TCM-herbal treatment next to conventional chemotherapy, may improve prognosis in advanced non-small-cell lung cancer patients ’

The fact that the improvement in prognosis is so similar, suggests that the common factor (herbal treatment) has overriding strong prognostic effect. Although the overall herbal treatment differed at certain points between the Chinese and USA studies, a number of the herbs used were the same. The lead time to treatment varies, roughly 1 month in McCulloch’s and 3 months in Guo’s study. Still, the results were very similar.

However, there are also weak points. The studies were not randomised before the studies started, but retrospective (McCulloch) or case-controlled (Guo). Also, the studies were not population-based. Self-selection of patients to TCM clinics may have caused significant selection bias: are the patients seeking herbal treatment those with a healthier life style, or do they have a socio-economically better survival probability? Guo et al argue in the discussion of their study that this is not likely the case in their patients, but final proof is not available.[13]

It has been argued that the improved prognosis of TCM treated patients is merely due to the better access that more educated, economically well-to-do patients have to such treatments, and hence social differences affecting these aspects. Better-off patients could simply afford to pay for eventual additional treatment and therefore have better access to top quality conventional treatments (e.g. target therapy), or perhaps live in a better social environment with better palliative terminal care. In support of this hypothesis it has recently been shown that early integrated palliative terminal care significantly influences the survival of terminal patients.[40] However, we have argued that socio-economic or racial differences between our TCM and control groups can be regarded as excluded,[13] thereby strengthening the hypothesis that TCM herbal treatment is really effective in metastatic lung cancer.

Another explanation could be that TCM herbal treatment has no effect on the metastatic tumour cells at all but prolongs survival by improving the QOL (emotional functions, cognitive functions, nausea and vomiting) or special lung cancer-related symptoms (coughing, phlegm, short of breath, fatigue amongst others).[65,66] Although one exploratory study found TCM may worsen QOL and survival, the majority of evidence is favourable. This might in turn motivate patients in such a manner that their will to live is strengthened. The resulting better feeding status could perhaps also prolong survival if the patient would favour more than the tumour cells.

One can therefore not regard the studies as definitive. Rather, they are suggestive and encouraging.

Steps to be taken to get reliable unequivocal results
Medical oncologists and herbal medicine specialists using integrative medicine techniques should spend much effort in the coming years to obtain undeniable proof that TCM treatment of metastatic highly malignant cancers ‘really helps’, i.e. can be regarded as ‘scientifically sound’. It is therefore important to consider which phase 1, 2 and 3 trials should be undertaken.

First, there is the intriguing lack of prognostic effect of TCM syndrome differentiation in Guo’s study. While this may be due to issues with reproducibility, it is also possible that herbal treatment according to TCM syndrome effectively eliminates the possible negative prognostic effects of particular syndromes. In China, TCM syndromes certainly dictate the herbal combinations to be given to different patients, and trials should thus at least balance the distribution of TCM syndromes among groups, or be restricted to a single TCM syndrome to equalise the herbal treatments to be applied. An initial study should assess distribution of TCM syndromes in the potential study population and assure reproducibility of syndrome differentiation among the study physicians responsible for TCM treatment.

Secondly, there is the problem of efficacy of individual herbs. As a chemical formula for the effective components is lacking for most herbs, one must rely on therapeutic effect of the herbs ‘by experience’. However, it is exactly the experience of many TCM doctors that the same herbs may not always be equally effective. This may be due to the variable quality of the same herb produced by different manufacturers, and even when carefully controlled under good agricultural practice of the same company, variability may be due to seasonal or climatic variations of the herb's effective component. It is therefore of the utmost importance that food and herb international preparation and testing guidelines be developed, and strictly followed.

Thirdly, formal phase 1 trials should assess the safety and potential for adverse herb-drug interactions of the herbal formulas to be used with conventional chemotherapy-treated patients as controls. Although this seems futile to Chinese TCM doctors who have long observed that the side effects of TCM herbal treatment are minimal, it is important to have formal validation for this in the Western world. Animal experiments are also of importance.

Fourthly, a large multi-centre prospective randomised, preferably population-based, trial should be undertaken in patients with advanced non-small-cell lung cancer, comparing standardised conventional platinum-based chemotherapy (PBT), versus PBT plus TCM herbal treatment. The stage, performance score, gender, neuro-endocrine, radiologic and immune status of the patients should be known before, during and after treatment. Moreover, the radiology, pathology and preferably also EGF-R mutation status, steroid receptor status and immune profile of the primary tumour should be known. A similar prospective trial also including targeted therapy should be performed. Regular controls of the above mentioned neuro-endocrinological and immune parameters and objective diagnosis criteria by radiologic and pathologic data are mandatory. There should not be the slightest doubt about the initial inclusion criteria.

What to do with NSCLC patients until such definitive results are available?

An answer to the question of how to counsel NSCLC patients until such definitive results are available depends on different factors, which may vary from one country to the other. The following therefore cannot be anything other than widely useful considerations for discussions with patients, and not absolute guidelines.

There are the legal aspects for doctors giving TCM integrative therapy. It is well known that many patients with metastatic cancer use over-the-counter herbs, vitamins and food supplements, irrespective of what their treating doctor says. It is important for clinicians to realise they may be encountering desperate patients willing to do anything to prolong survival and improve QOL.

Since providers of TCM are commonly seen as providing supportive care, they are in a unique position to encourage patients with terminal disease to consider the benefits of early palliative care offered by physician providers.[64] Integrative therapy can provide powerful psychological effects, and help strengthen the patient's optimism: it is known that dispositional optimism predicts survival in some cancers.[68] This can intentionally harness the placebo and nocebo effects, both of which may have an effect on quality of life. Patients can be counselled that chromosomes are not their fate but that diet, lifestyle and psyche can change gene expression, such as telomere length specifically in prostate cancer.[69]

While the data in this area are not yet sufficient to provide guidelines for patient counselling, the studies we review provide encouragement to further investigate the role of TCM integrative therapy. Many of the aspects of clinical trial design regarding such investigation are clear from prior work, and we hope that progress will be made toward relevant trials in the near future.

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