Chinese Medicine for People with Lung Cancer: Treatment Results

Clinical Advocacy Conference, Commonweal 2012

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Historical origins

- Chinese medicine developed within the context of the social, political, and geographical milieu of the growth and development of China throughout its history.
- Incorporation of newly discovered medicines from other parts of the world into the broader framework of the practice of medicine.
- Examples include influences from Indian Ayurvedic medicine, Persian-Islamic influences via the Silk Road

Philosophical origins

- Taoism: health is becoming harmonious with nature, emphasizing the extra channels and Heart-Kidney connection
- Buddhism: health means accepting who you are, emphasizing sedation and strategies and Heart-Spleen harmonization
- Confucianism: health means knowing who you are relative to the social hierarchy, emphasizing tonic strategies and Liver-Spleen-Kidney harmonization

Relevant case information

- Western medical history of the present illness
- Laboratory results & pathology report
- Imaging reports
- Exercise history
- Dietary history
- Family history
- Review of current stresses and other demands
- Chinese medical history
- Pulse & diagnosis
- Review of symptoms and signs

3-week treatment timing

Part 1: begins the day of chemotherapy infusion, and continues through Day 3

- potentiate chemotherapy effectiveness
- enhanced systemic drug delivery by improving circulation and reducing muscle tension

Part 2: days 4 through 11

- help cleanse the system of toxic (but no longer therapeutically active) drug metabolites
- help cleanse the lymphatic system

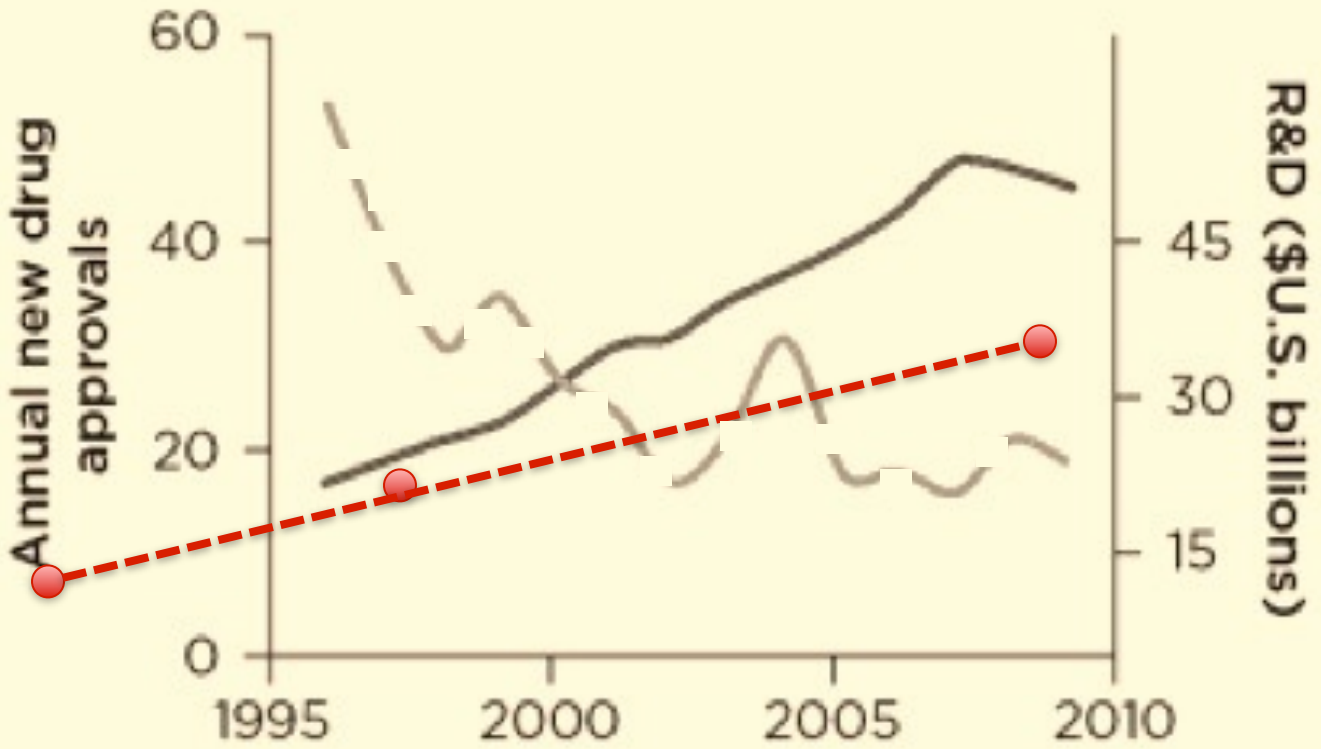
Part 3: days 12 until the day of next chemotherapy infusion

- systematically rebuild the immune system
- prepare the liver,kidneys and bone marrow for the next round of chemotherapy

We conducted a survival study with 10-year follow-up of lung (n=235) & colon cancer (n=193) patients

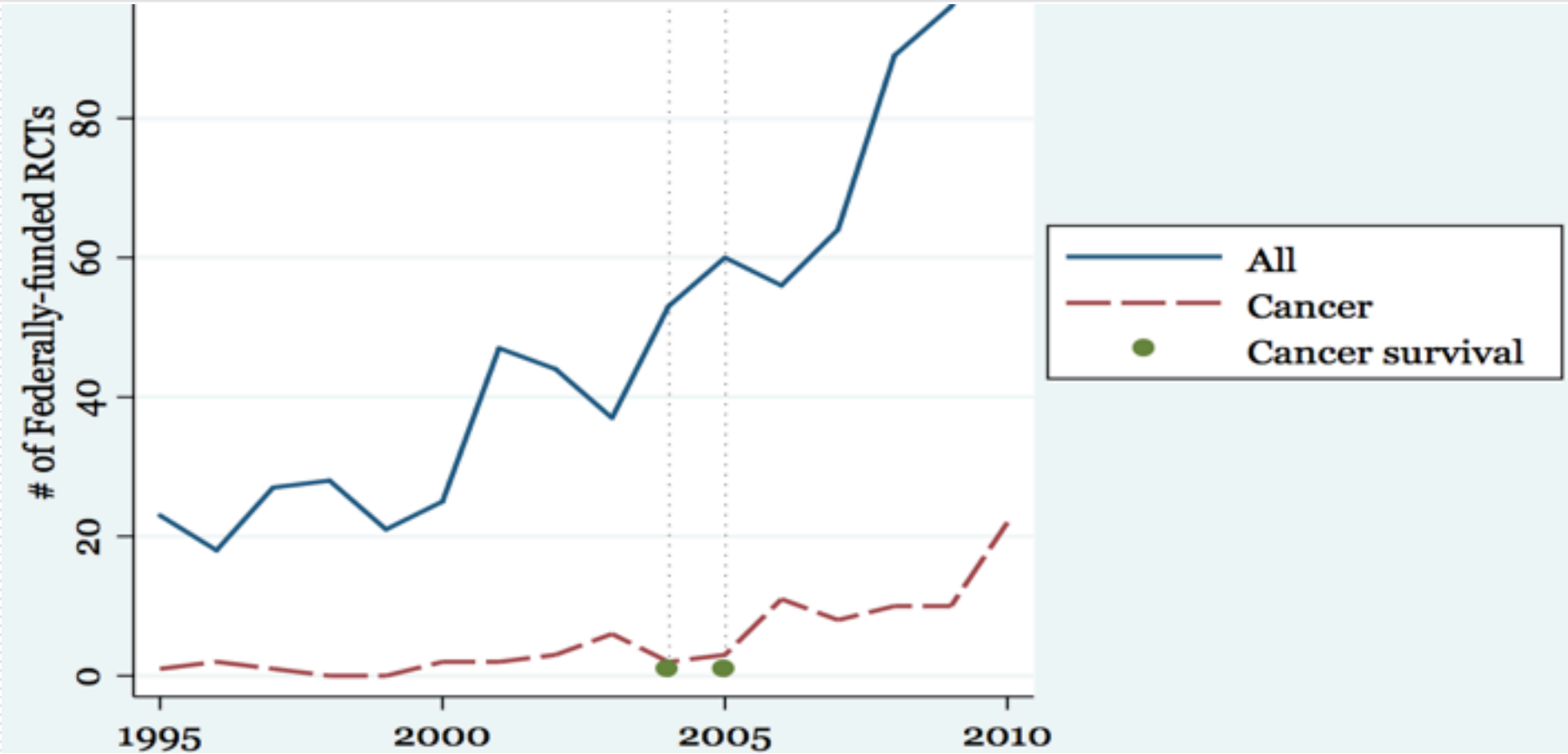
- Retrospective medical record data
- Diagnosis: biopsy/pathology reports, x-ray, CT
- Patients treated at a Chinese medicine clinic, also receiving care at regional oncology centers
- Consecutive case series: all patients with lung or colorectal cancers presenting between 1986 and 1993
- Internal comparison:
  - patients following treatment only during chemotherapy/ radiation therapy (short-term), vs.
  - those who continued (long-term)
- External comparison:
  - our cohort vs.
  - cancer registries (Kaiser Permanente & California Cancer

Growth in CAM use may be outpacing growth in pharmaceutical development



(Eisenberg, Davis et al. 1998; Nahin & Dahlhamer, et al. 2010; Stockwell, 2011)

Very few federally-funded randomized CAM cancer trials have been published



(Source: PubMed systematic search, 1995-2010, NHS/NCI/NCCAM grants, all RCTs)

Randomized trials can show inflated therapeutic benefit compared to real-world use

- In meta-analyses comparing RCTs to observational studies, RCTs showed exaggerated benefits in:
  - Antidepressants in major depressive disorder: a 5-fold inflation of drug benefits (Naudet & Maria, et al. 2011)
  - Drugs to reduce bleeding during angioplasty: a 2-fold inflation of drug benefits (Centurión, 2010)
- In a meta-analysis of 110 RCTs: Primary outcomes changed in 34% of trials, and secondary outcomes in 70%, between time of trial registration & publication. (Ewart & Lausen, 2009)
- Clinical trial protocols may exclude as many as 60% of patients who would otherwise be eligible for a therapy in community care practice (Gandhi & Ayanian et al. 2005)

Patient recruitment in CAM trials faces huge obstacles, limiting feasibility of RCTs

- **Less than 3% of cancer patients will participate in randomized trials** (Murthy & Krumholz, et al. Jama 2004)
- **This may even be more so the case with CAM trials, because CAM therapies are so widely available.**
- **Many CAM therapeutic approaches show positive data in observational studies, but RCTs are proceeding very slowly, and other questions may never be answered, or answerable, by RCTs.**
- **Question: are randomized trials really the best way to evaluate CAM efficacy?**

Observational (non-randomized) studies & RCTs: both have advantages & limitations

	RCTs	Observational studies
Cost	Very high; also vulnerable to financial interest bias	Very low
Selection bias	Overly selected patients	Wealthier (but sicker) patients often select CAM
Feasibility	Patients recruitment for CAM trials difficult	Very high (data already exist)
Internal validity	Less confounding by unmeasured variables.	Analysis relies more on breadth of data
External validity	Highly constrained clinical context	More representative of how CAM is used in practice

Marginal Structural Models (MSMs) & Propensity Score: help reduce selection bias in analysis of observational data (very

- Can provide near-randomized comparability between groups in observational studies (given enough variables that could contribute to the outcome).
- Particularly important in self-selected treatment setting.
- Reduce bias by adjusting for confounding
- Can identify true causal effects sometimes not found through traditional association models
- A standardization tool, making groups comparable based on probability of having been treated, given individual characteristics, such as age, gender, and other variables

Study population

		Short-term tx lasting duration of chemotherapy/ radiation	Long-term continuing after chemotherapy/ radiation	Total
Lung Cancer		**54**	**181**	**235**
Stage	II	11	22	33
Stage	IIIA	9	66	75
Stage	IIIB	13	71	84
Stage	IV	21	22	43
Colon Cancer		**36**	**157**	**193**
Stage	I	7	12	19
Stage	II	7	39	46
Stage	III	11	47	58
Stage	IV	11	59	70

Stage IV lung cancer: patients

	PAM+V	CCR	KPNC	Total
Stage IV (number of participants)	43	6079	560	6682
Median age (years)	61	66	64	66
Treated with surgery (%)	0	7	10	7
Treated with chemotherapy (%)	100	33	21	33
Treated with radiation (%)	0	64	62	64
Female (%)	30	39	43	40
Adenocarcinoma (%)	79	67	72	68
Squamous cell carcinoma (%)	21	32	28	32
White (%)	95	87	73	86
Black (%)	2	8	12	9
Asian (%)	2	5	8	5
Hispanic (%)	0	0	7	1

Abbreviations: PAM+V, Pan-Asian medicine + vitamins; CCR, California Cancer Registry; KPNC, Kaiser Permanente Northern California.

(Broffman & McCulloch, et al. Integrative Cancer Therapies, Aug 2011)

Stage IV colon cancer: patients

	PAM+V	CCR	KPNC	Totals
Stage IV (number of patients)	70	1914	462	2446
Median age (years)	63	71	67	70
Female (%)	33	51	46	50
Adenocarcinoma (%)	99	86	86	86
Squamous cell carcinoma (%)	1	14	14	14
Treated with surgery (%)	96	80	79	80
Treated with chemotherapy (%)	100	45	55	48
Treated with radiation (%)	6	5	12	6

Abbreviations: PAM+V, Pan-Asian medicine + vitamins; CCR, California Cancer Registry; KPNC, Kaiser Permanente Northern California.

(Broffman & McCulloch, et al. Integrative Cancer Therapies, Aug 2011)

Treatment details: lung cancer study

	Daily Dose	Part I Days 1-3	Part II Days 4-8	Part III Days 9-20
Thymic protein	1 packet			✓
N-acetyl cysteine	600-1800 mg			✓
Siberian ginseng extract	250-1000 mg		✓	✓
Panax ginseng extract	250-1000 mg		✓	✓
Curcumin	500-1000 mg		✓	✓
Spirulina	1-5 gm		✓	✓
Germanium sesquioxide	30-100 mg		✓	✓
Co-enzyme Q-10	90-150 mg		✓	✓
Garlic extract	300-1200 mg		✓	✓
Ginkgo biloba extract	60-180 mg		✓	✓
Green tea beverage	1-5 cups		✓	✓
Grapeseed extract	50-150 mg		✓	✓
Antioxidant combo (Vits A, B-complex, B-12, C, D, E, Folic acid, Selenium and Zinc)			✓	✓
Melatonin	3-20 mg	✓	✓	✓
Acidophilus	1-3 caps	✓	✓	✓
Chinese herbal formula	See below	✓	✓	✓
Fish oil	3-10 gm	✓	✓	✓
Shark or bovine cartilage	300-1200 mg	✓	✓	✓

(Broffman & McCulloch, et al. Integrative Cancer Therapies, Aug 2011)

Integrative Cancer Therapies
XX(X) 1–20

DOI: 10.1177/1534735411406439
http://ict.sagepub.com
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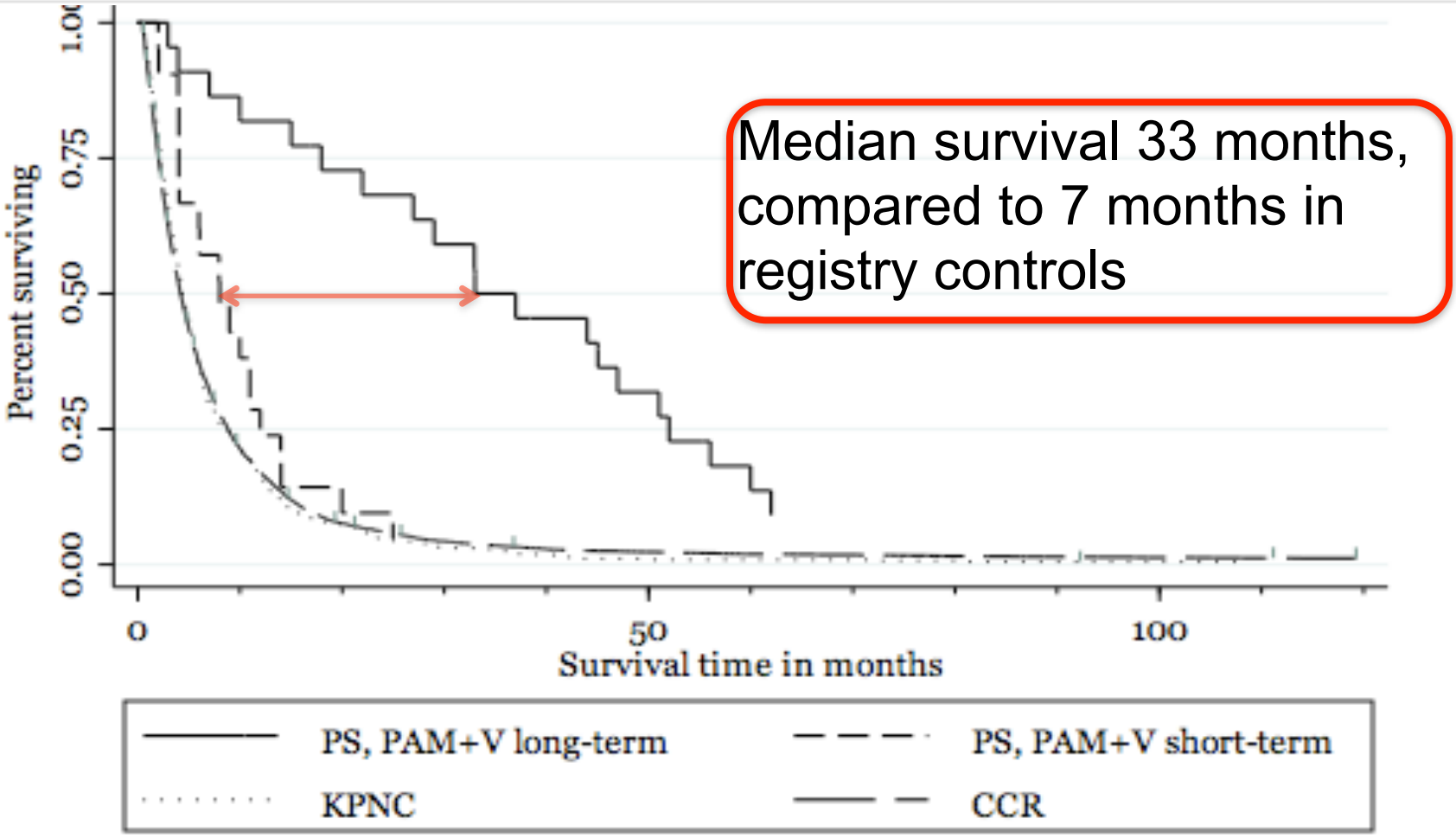
In adjusted analysis with Propensity Score balancing, herbal medicine and multivitamins combined with conventional therapy compared with conventional therapy alone, improved survival by:

- Stage IIIA (n=75) by 46%
- Stage IIIB (n=84) by 62%
- Stage IV (n=43) by 69%

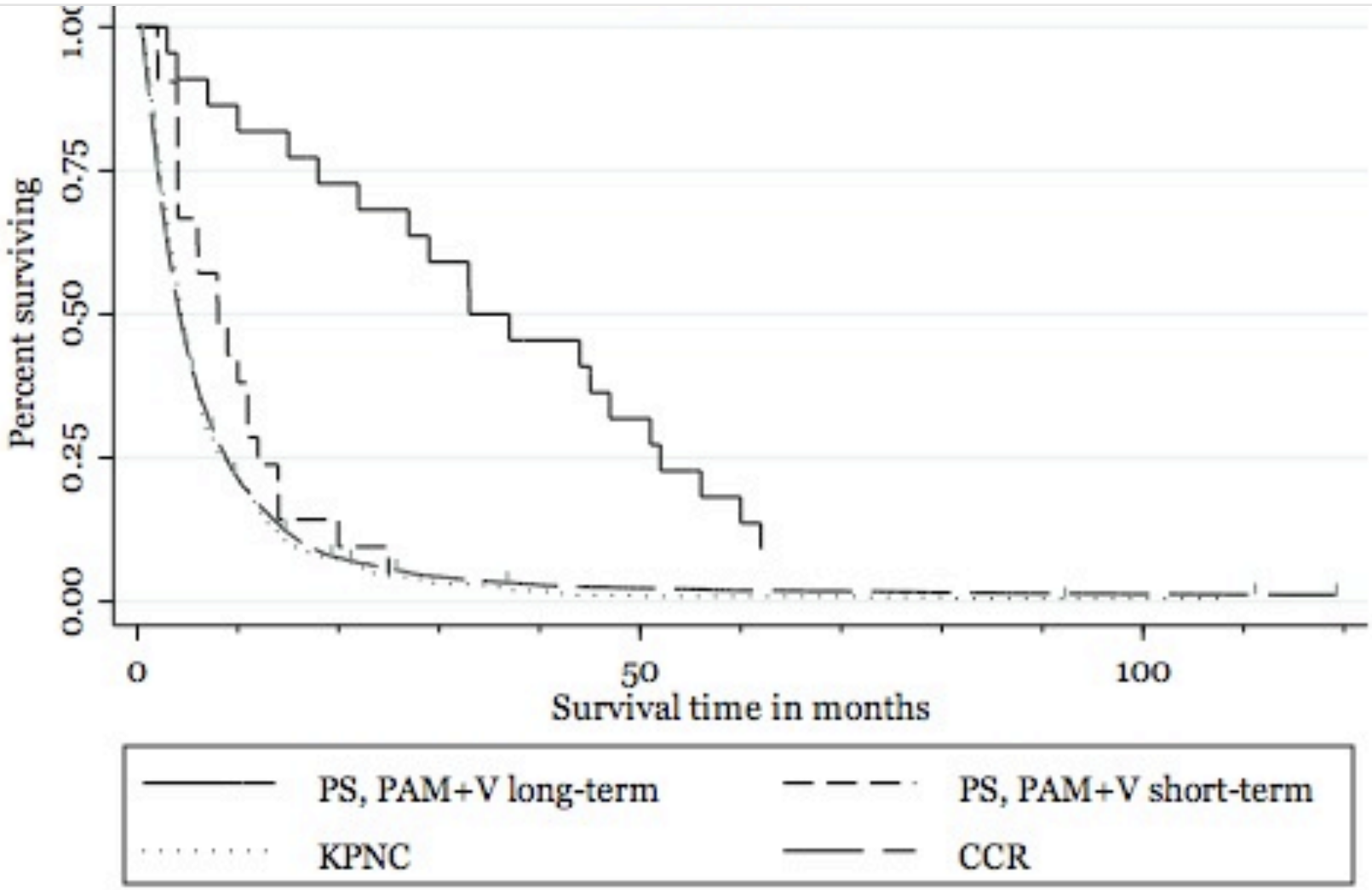
Stage IV Lung Cancer: Herbs & Vitamins +



Median survival 33 months, compared to 7 months in registry controls

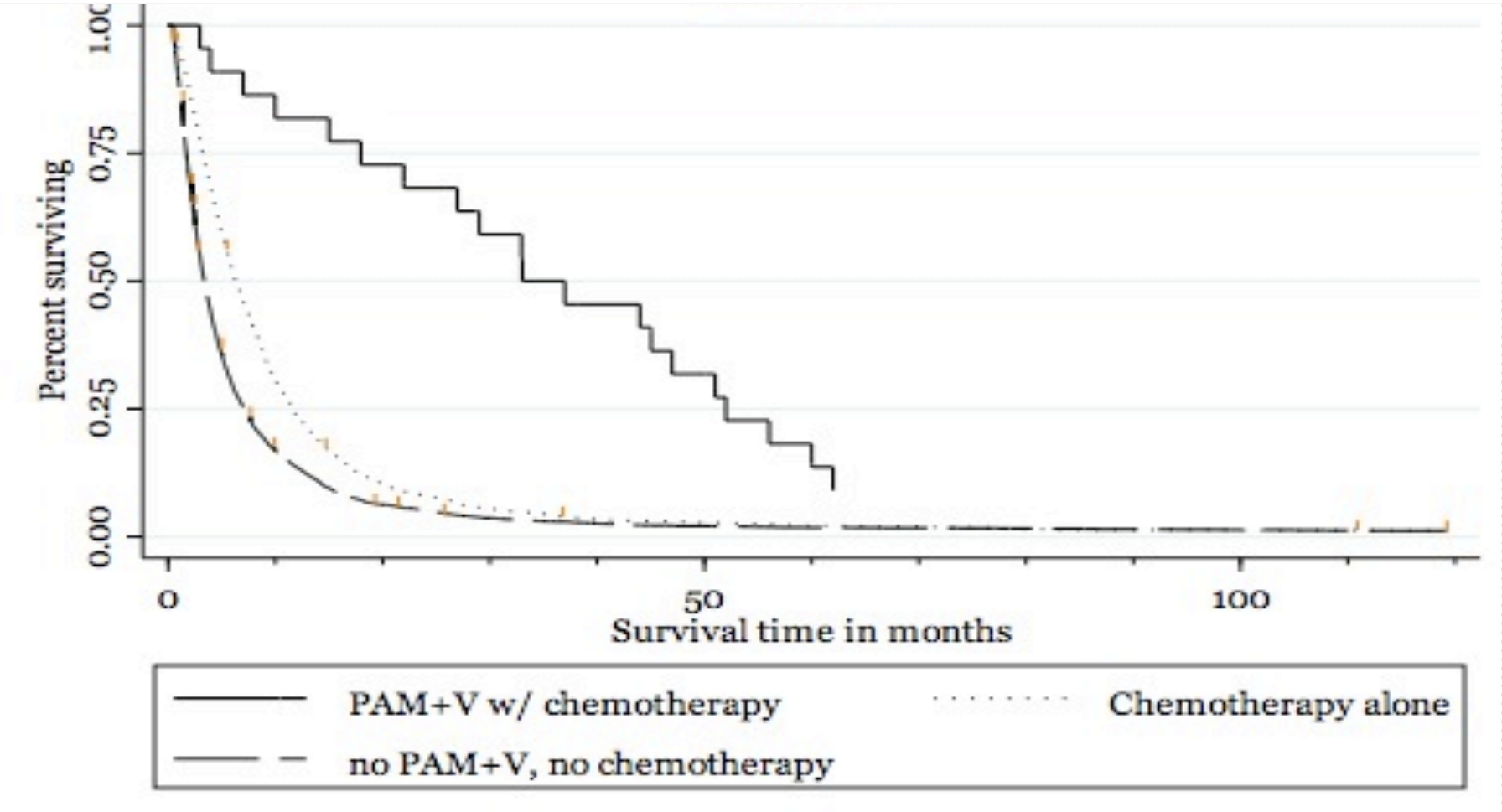
(PAM+V = Pan-Asian Medicine + Vitamins; KPNC = Kaiser Registry, CCR = California Cancer Registry)

Stage IV Lung Cancer: how long should supportive care continue?



(PAM+V = Pan-Asian Medicine + Vitamins; KPNC = Kaiser Registry, CCR = California Cancer Registry)

Stage IV Lung Cancer: herbs & vitamins, with or without chemotherapy



(PAM+V = Pan-Asian Medicine + Vitamins)

Stage IIIA Lung Cancer: herbs & vitamins, with or without radiation

Stage IIIA Lung Cancer: herbs & vitamins, with or without surgery

Herbs & vitamins: is it the medicine, or where it's delivered?

1, 2 and 5-year survival rates: lung cancer

	Long-term PAM+V	Short-term PAM+V	Kaiser Permanente	California Cancer Registry
Stage II				
1 Year	95%	100%	64%	67%
2 Year	77%	82%	37%	44%
5 Year	36%	36%	13%	22%
Stage IIIA				
1 Year	93%	70%	50%	47%
2 Year	83%	44%	23%	25%
5 Year	32%	22%	8%	11%
Stage IIIB				
1 Year	89%	23%	34%	29%
2 Year	72%	15%	11%	12%
5 Year	24%	0%	5%	4%
Stage IV				
1 Year	82%	24%	16%	17%
2 Year	60%	10%	4%	6%
5 Year	14%	5%	1%	2%

(PAM+V = Pan-Asian Medicine + Vitamins)

Lung cancer, long-term vs short-term tx: strong survival advantage remains in adjusted analysis

CHM+V long vs. short-term	Stage II		Stage IIIA		Stage IIIB		Stage IV	
# subjects (CHM+V long-term)	22		66		71		22	
# subjects (CHM+V short-term)	11		9		13		21	
Cox regression, unadjusted	0.77	[0.36, 1.67]	0.82	[0.40, 1.69]	0.21^{***}	[0.11, 0.40]	0.32^{***}	[0.17, 0.62]
Cox regression, adjusted	0.73	[0.30, 1.79]	0.49	[0.21, 1.11]	0.17^{***}	[0.08, 0.36]	0.28^{**}	[0.13, 0.60]
Propensity score Cox, unadj	0.75	[0.30, 1.83]	0.85	[0.40, 1.81]	0.28^{***}	[0.14, 0.56]	0.29^{**}	[0.14, 0.61]
Propensity score Cox, adj	0.82	[0.32, 2.11]	0.50	[0.22, 1.14]	0.17^{***}	[0.08, 0.36]	0.28^{**}	[0.12, 0.61]
MSM Cox regression	0.78	[0.39, 1.59]	0.82	[0.17, 3.94]	0.47	[0.10, 2.31]	0.26	[0.01, 4.25]

www.pinestreetfoundation.org

Lung cancer, long-term vs registry controls: strong survival advantage remains in adjusted analysis

Long-term CHM+V vs. KPNC	Stage II	Stage IIIA	Stage IIIB	Stage IV
# subjects (PAM+V)	22	66	71	22
# subjects (KPNC)	89	137	115	560
Cox regression, unadjusted	0.64 [0.40, 1.01]	0.42^{***} [0.31, 0.57]	0.32^{***} [0.24, 0.44]	0.27^{***} [0.17, 0.42]
Cox regression, adjusted ▲	0.63 [0.37, 1.06]	0.27^{***} [0.17, 0.43]	0.26^{***} [0.16, 0.40]	0.25^{***} [0.16, 0.40]
Propensity score Cox, unadjΦ	0.64 [0.37, 1.11]	0.40^{***} [0.25, 0.63]	0.38^{***} [0.22, 0.65]	0.21^{***} [0.12, 0.37]
Propensity score Cox, adjΦ▲	0.61 [0.35, 1.07]	0.29^{***} [0.18, 0.46]	0.34^{***} [0.19, 0.59]	0.22^{***} [0.12, 0.39]
MSM Cox regression Ω	0.66 [0.30, 1.03]	0.40^{***} [0.30, 0.52]	0.14^{***} [0.07, 0.28]	0.25^{**} [0.08, 0.41]

Alternate Explanations for these Survival Differences

- Selection bias: are patients who are choosing CAM better off to begin with?
- Higher social and economic status: associated with less smoking, longer survival
- Self-efficacy (making better choices for yourself leads to better outcomes): difficult to measure retrospectively
- Informative censoring: did patients with worse prognosis not continue treatment?
- Residual confounding: other factors which contributed to the outcome?

Lung cancer & herbs: meta-

Astragalus-Based Chinese Herbs and Platinum-Based Chemotherapy for Advanced Non–Small-Cell Lung Cancer: Meta-Analysis of Randomized Trials

Michael McCulloch, Caylie See, Xiao-juan Shu, Michael Broffman, Alan Kramer, Wei-yu Fan, Jin Gao, Whitney Lieb, Kane Shieh, and John M. Colford Jr

Twelve studies (n = 940 patients): reduced risk of death at 12 months (RR = 0.67; 95% CI, 0.52-0.87).

Thirty studies (n = 2,472): improved tumor response (RR = 1.34; 95% CI, 1.24 to 1.46).

Acknowledgements. We express our appreciation to the following:

- Mark Renneker MD & Sandee Birdwell MD
- Our co-authors:
  - Michael Broffman LAc (Pine Street Foundation)
  - Mark van der Laan, PhD (University of California Berkeley)
  - Alan Hubbard, PhD (University of California Berkeley)
  - Lawrence Kushi, DSc (Kaiser Permanente Northern Calif.)
  - Alan Kramer, MD (San Francisco Oncology Associates)
  - Donald I. Abrams, MD (San Francisco General Hospital, University of California San Francisco)
  - Jin Gao, MD, PhD (Chinese Academy of Sciences, Beijing)
  - John M. Colford Jr, MD, PhD (University of California Berkeley)
- California Cancer Registry

Conclusions

- Consecutive case series: everyone case counted.
- Lag time: ruled out with sensitivity analysis.
- Propensity Score & MSM methods: allow causal inference, and address selection bias.
- Whole Systems comprehensive treatment.
- Significant survival benefit.
- "Low-tech methods" for analyzing "low-tech medicine", at lower cost than