

A scenic landscape photograph of a valley. In the foreground, there is a green lawn. Behind it, a dense line of trees, including tall willows and other leafy trees, stretches across the frame. In the background, a range of mountains with some greenery and some bare patches is visible under a blue sky with scattered white clouds. The overall scene is bright and natural.

Chemoprevention of GU Cancer

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Background

- Cancer is the leading cause of death in the United States, above heart disease and medical mistakes
- Most cancers have a latency of 10-20 years
- Chemoprevention: suppress or reverse malignant transformation, reduce initiation (blocking agents) or promotion (suppressive agents)

Potential Agents

- Ideal agents would be safe, inexpensive and effective
- Dietary agents, eg. vitamins, minerals
- Drugs, eg. nonsteroidal anti-inflammatory agents, immune stimulants, ? Statins?

GU Cancers Potentially Amenable to Chemoprevention

- Bladder cancer: long risk for tumor recurrence; long latency
- Prostate cancer: high incidence, protracted course
- Renal cell carcinoma
- Testicular cancer

Progress in Bladder Cancer

- Incidence up from 14.6/100,000 in 1973 to 16.5 in 1997 (adjusted to 1970 population)
- Mortality down from 4.2/100,000 in 1973 to 3.2 in 1997; 5 yr survival 53% in 1950, 82% 1997
- One of only 5 cancers (Testis -5.1; Bladder -1.3; Breast -.3; Ovary -.5; Thyroid -1.1) with *increased* incidence and *reduced* mortality

SEER, 2000

Bladder Cancer

Initial Stage (SEER) 1973-1996

- Localized: 66,430 patients (72.8%)
- Regional (incl. extravesical): 17,129 (18.8%)
- Metastatic: 2,759 (3.0%)
- Unknown: 4,927 (5.4%)
- **Considering known stages: 3.2% are metastatic, 20% are T3,T4, or N+, and 77% are CIS,Ta-T2**

Rabbani F: J Clin Onc. 19:94-100, 2001

Bladder Cancer

Initial Grade (SEER) 1973-1996

- Grade 1: 16,884 (18.5%)
- Grade 2: 32,049 (35.1%)
- Grade 3: 24,065 (26.4%)
- Grade 4: 6,612 (7.2%)
- Unknown: 11,635 (12.8%)
- **Of known grades: 61.5% low grade (1-2),
38.5% high grade (3-4) (J Clin
Onc. 19:94-100, 2001)**

Bladder Cancer: Natural History

- About 70% present with resectable, superficial tumors, but up to 88% recur by 15 yrs.
- Patients can and should be monitored with cystoscopic examination at frequent intervals to directly assess disease status
- Urine Cytology and other markers are available
- Accessible for disease assessment, topical and systemic treatment

Bladder Cancer: Natural History

- Tumor “recurrence”: new tumors from widespread mutations, seeding at the time of surgery, & /or incomplete resection
- Monoclonal disease: uniform X chromosome inactivation,* identical chromosomal aberrations in multiple tumors in 80% or more tumors**

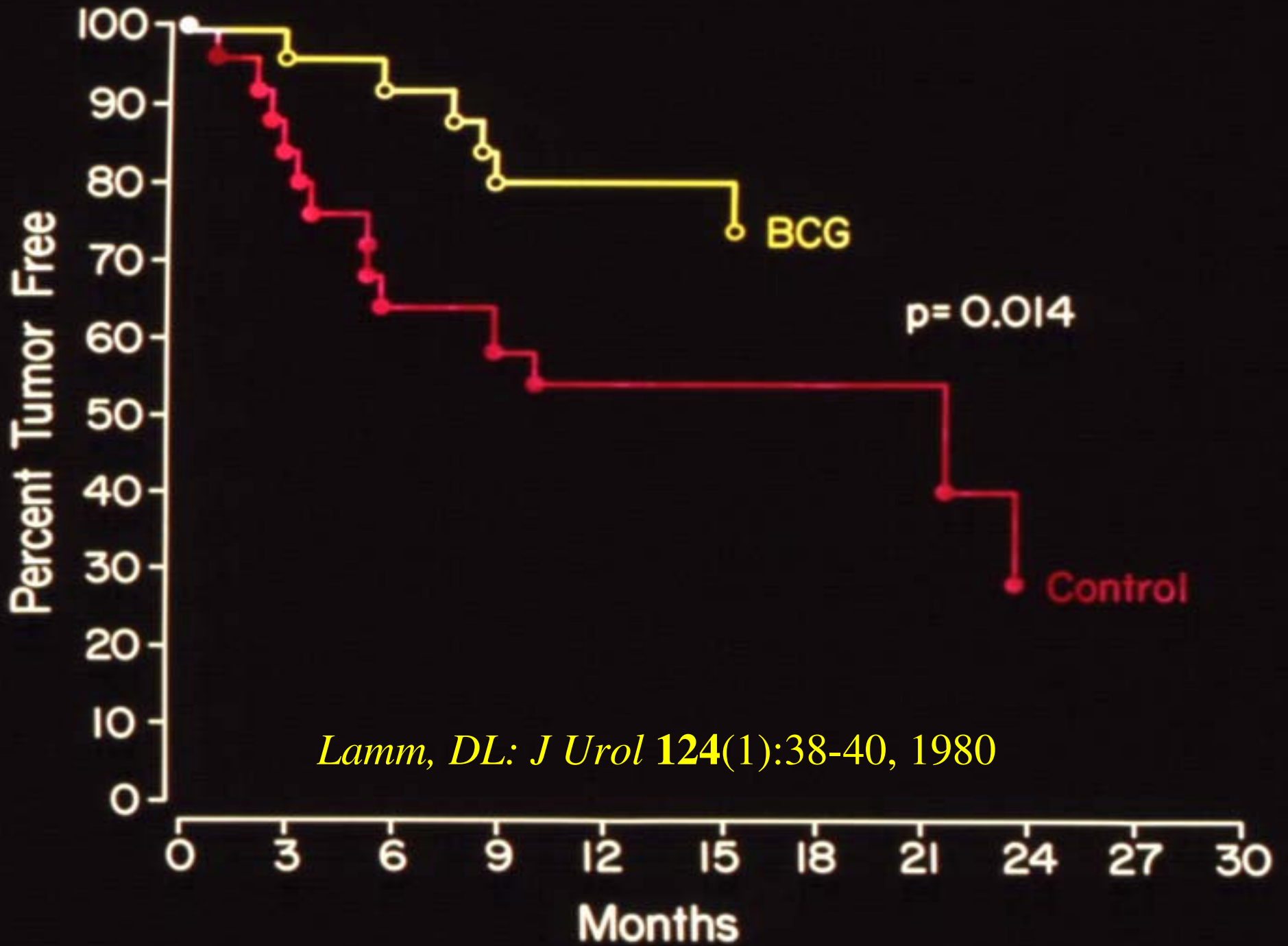
*Sidransky, NEJM 1992;**Simon, Ca Res 2001; Takahashi, Ca Res 1998

Progress in the Treatment of Bladder Cancer, Related to:

- Cisplatin-based chemotherapy, but median survival is only 12.3 months and only 7% survive 5 yrs (Loehrer. JCO 1992;10:1066)
- Improved intravesical therapy, but reduction in progression and mortality are difficult to prove
- Improved survival with cystectomy, but 5 year survival is only 45% (Dalbagni. J Urol 2001; 165:1111)

BCG in Bladder Cancer

- 1976: Morales- 12 fold reduction in recurrence in 9 bladder cancer patients
- 1977: Lamm reports success in controlled animal studies of bladder cancer
- 1980: Lamm reports successful randomized clinical trial
- 80's-90's: Multiple comparison studies show BCG to be superior to chemotherapy



Lamm, DL: J Urol 124(1):38-40, 1980

Summary of Controlled Chemotherapy Trials

Agent	series/N	% Δ (range)	<0.05
Thiotepa	1257/11	16.6% (-3-41)	6/11
Doxorubicin	1751/8	16.2% (5-39)	4/8
Mitomycin	1384/6	13.9% (1-42)	3/6
Ethoglucid	226/1	20.0%	1/1
Epirubicin	985/6	19.6% (9-26)	3/6
Total:	2297/32	17% (-3-42)	17/32

Controlled BCG Trials

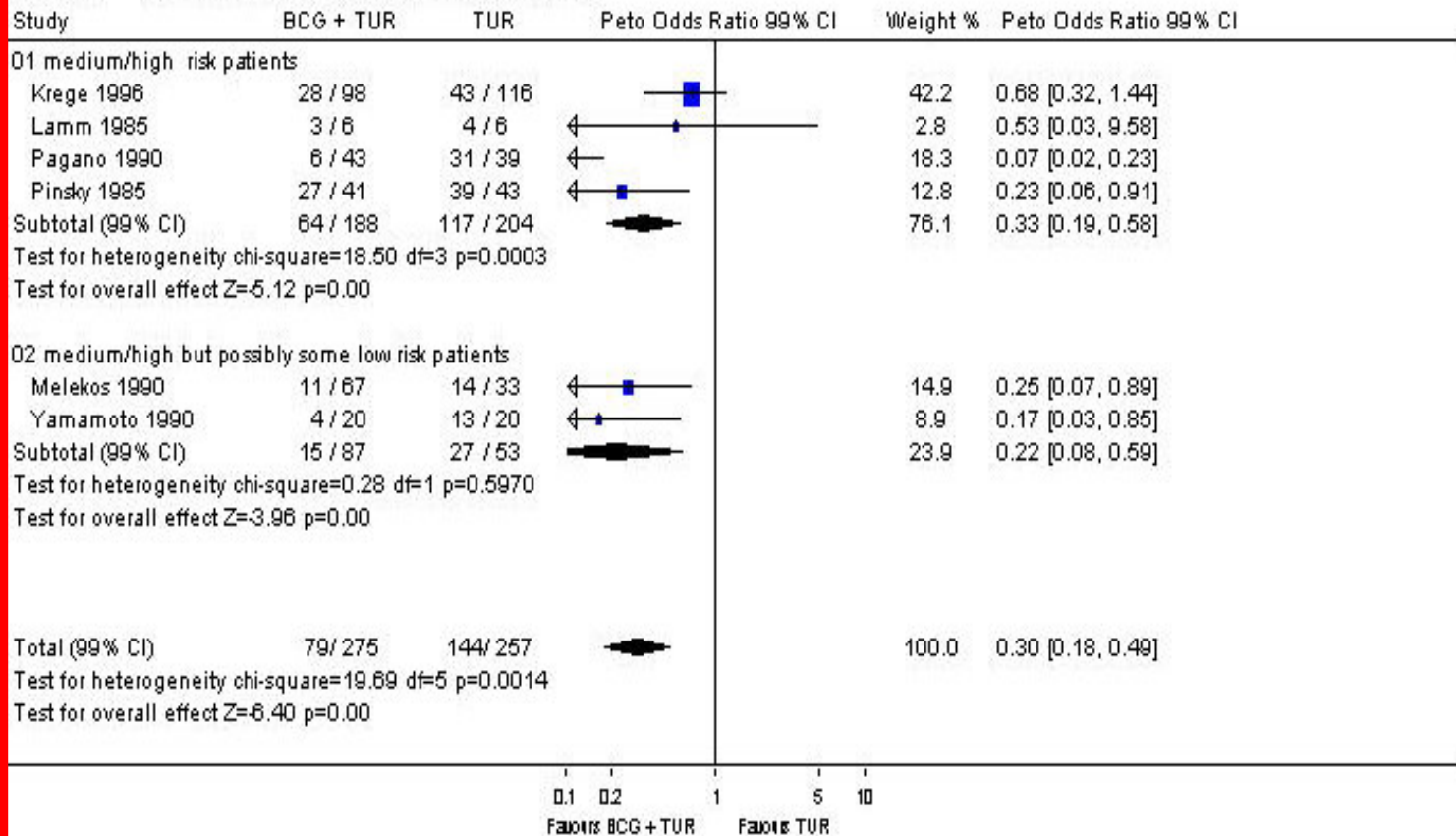
<u>AUTHOR</u>	<u>NO.</u>	<u>No Rx</u>	<u>BCG</u>	<u>BEN.</u>	<u>P</u>
Lamm ' 85	57	52%	20%	32%	<.001
Herr ' 85	86	95%	42%	53%	<.001
Herr (CIS) ' 86	49	100%	35%	65%	<.001
Yamamoto' 90	44	67%	17%	50%	<0.05
Pagano ' 91	133	83%	26%	57%	<.001
Mekelos ' 93	94	59%	32%	27%	<0.02
Krege' 96	<u>224</u>	<u>48%</u>	<u>29%</u>	<u>24%</u>	<u><0.05</u>
TOTAL:	687	72%	28%	44%	

Forrest Plot- Odds Ratio

Review: Intravesical Bacillus Calmette-Guerin in Ta and T1 Bladder Cancer

Comparison: 01 BCG + TUR versus TUR

Outcome: 01 number of patients recurring at 12 months



Shelley M, et al. Cochrane Database of Systematic Reviews

Summary: Cochrane Meta-analysis: TUR + BCG vs. TUR-Only

- HR=44%
- OR=31%
 - EER=28.7% @ 12 months
 - CER=56.3% @ 12 months
- ARR=27.6% @ 12 months
- **NNT= 4**
- **95% CI 2 - 6**

	Tumor	No Tumor	Total
TUR + BCG	79	196	275
	a	b	a+b
TUR Only	144	113	257
	c	d	c+d
Total	223	309	532
	a+c	b+d	a+b+c+d

How good is an NNT of 4 at 1 year?

- Insulin to prevent neuropathy in DM₁
NNT=**15**@ 6 yrs
- Streptokinase to prevent mortality after MI
NNT=**19** @ 5 wks
- Finasteride to prevent surgery for BPH
NNT=**18** @ 4 yrs
- Finasteride to prevent Cancer (PCPT)
NNT=**17**@ 7 yrs
- Radical Prostatectomy to prevent death from CA
NNT= **16** @ 8 yrs

Smoking Cessation in Bladder Cancer

Fleshner. J Urol 161:172, 1999

- 286 Ta, T1 pts between 1985 and 1995
- Ex smokers present at an older age (64) than current smokers (59), with no difference in stage or grade
- Recurrence-free survival increased among those who quit smoking ($P=0.03$)
- Progression-free survival increased among those who quit smoking ($P<0.01$)

Agents for Bladder Cancer Chemoprevention

- **Vitamins: A, B6, C, D, E, folic acid, C+K3** (A: Sporn'79, Moon'83; B6: Byar'77, C: Schlegel'75, D: Konety'01; E: Michaud'00; C+K3: Gilloteaux'98)
- **Allium sativum** (Lau'86, Riggs'97, Lamm'01)
- **NSAIDS** (Goodwin'81, Waddell'83, Earnest'92, Moon'92)
- **DMFO** (Messing'88, Boone'90, Kellog'92, Loprinzi'96)
- **Oltipraz** (Wattenberg & Buening'86, Moon'94, Kensler'95)
- **Selenium** (Helzlsouer'89)
- **Soy protein** (Mokhtar'88)



DOMINION DI TEMPAT LAIN
SELAIN DARIPADA KAWASAN NI
沒有執照零售酒類, 但不
得在此處飲用。
Selling wine and spirits
without a license is illegal
elsewhere.
IS LICENSED TO SELL BY RETAIL
INTOXICATING LIQUORS FOR
CONSUMPTION ELSEWHERE
THAN ON THIS PREMISES

Vitamin A

- Fat-soluble retinols and carotenoids that promote cell differentiation
- Trans-retinoic acid: causes differentiation of promyelocytic leukocytes, increases survival from 49 to 76% vs chemo alone (Fenaux & Degos: NEJM. 337:1076,1997)
- Stimulates immune response (Beisel: JAMA. 245:53,1981)

Vitamin A: Epidemiology

- Increased risk of bladder cancer with decreased intake of Vitamin A and low serum retinol (Mettlin C & Graham S. Am J Epid. 110:255,1979)
- Lower carotene and retinol levels vs Controls (Eichhozer M. Int J Ca. 66:145, 1996)
- Increased cancer mortality with low serum carotene (Hicks R: P Nutr Soc. 42:83,1980)

Vitamin A: Animal Studies

- Inhibits malignant transformation by chemical carcinogens or radiation
- Reduces carcinogen-induced cancer of the skin, breast, and bladder as well as esophagus, liver and cervix
- Most effective when given shortly after carcinogen exposure, but in bladder can be given as long as 9 weeks later

Vitamin A: Animal Studies

- Deficiency accelerates carcinogenesis
- Vitamin A derivatives potentiate the effect of immunotherapy with BCG (Pang & Morales'83)
- 13-cis retinoic acid and all trans-4-hydroxy-phenyl retinamide are effective, but 4-HPR appears to be better and less toxic (Moon: Carcinogenesis 3:1469,1982)

Vitamin A: Human Trials

- Evard and Bolag, 1972: 4 (27%) complete and 7 (47%) partial response in 15 patients
- Etreinate: reduced tumor recurrence from 87% to 60% (Alfthan, 1983) and in a second study delayed second recurrence from 13 to 20 months ($P < 0.006$) and annual recurrence from 2.1 to 0.95 ($P < 0.001$, Studer, 1995)

Vitamin A: Human Trials

- Fenretinide (4-HPR) in 149 randomized patients in SWOG multicenter study
- Fenretinide (23) failed to reduce compared to placebo (24), HR =0.94
- Treatment given for only 12 months

Lerner S. J Urol.173:913, May, 2005

Vitamin B6 (Pyridoxine)

- A coenzyme involved in amino acid and neurotransmitter metabolism
- Reduces carcinogenic metabolites of tryptophan that are associated with TCC: kynurenine, 3-hydroxy kynurenine, and 3-hydroxy anthranilic acid (Brown, Acta I Ca, 1960)
- Stimulates lymphocyte responses and enhances tumor immunity (Talbot, AJCN, 1997)

Vitamin B6: Human Trials

- VA Cooperative Study (Byar '77): 60% , 46%, and 47% recurrence in 118 randomized bladder tumor patients treated with placebo, B6, or Thiotepa (P<0.03 after first year) (Byar & Blackard: Urol. 10:556, 1977)
- EORTC: no advantage to B6 therapy in 291 randomized patients (Newling: Eur Urol. 27:110,1995)

Vitamin C (Ascorbic Acid)

- Potent reducing agent, water-soluble antioxidant and free radical scavenger
- Inhibits malignant transformation in vitro and decreases chromosome damage in lymphocytes exposed to bleomycin (Benedict, 1982; Pohl & Reidy, 1989)
- Increased dietary intake associated with reduced cancer of the mouth, esophagus, stomach, colon, lung and bladder (Nomura: Int J Cancer. 48:199,1991)

Vitamin C Animal Studies

- Associated with reduced formation of N-nitroso compounds, decreases cancer of the esophagus, stomach and bladder in rodents
- Some studies, however, have reported an increase in cancer (oral and bladder) associated with increased Vitamin C depending on dose and carcinogen

Vitamin C Human Studies

- Prospective therapeutic trials have failed to show an advantage to Vitamin C supplements
- In a cohort study of 11,580 subjects in a retirement community, bladder cancer was reduced in those taking Vitamin C

(Shibata, Br J Cancer. 66:673, 1992)

Vitamin E

- Lipid-soluble antioxidant, protects unsaturated lipids in cell membranes and enzymes such as coenzyme Q from free radical oxidation
- Curbs generation of toxic peroxidation products
- Like ascorbic acid, E reduces carcinogenic N-nitroso compounds
- Inhibits smooth muscle and cancer cell growth
- Increased resistance to infection, DTH and Ab

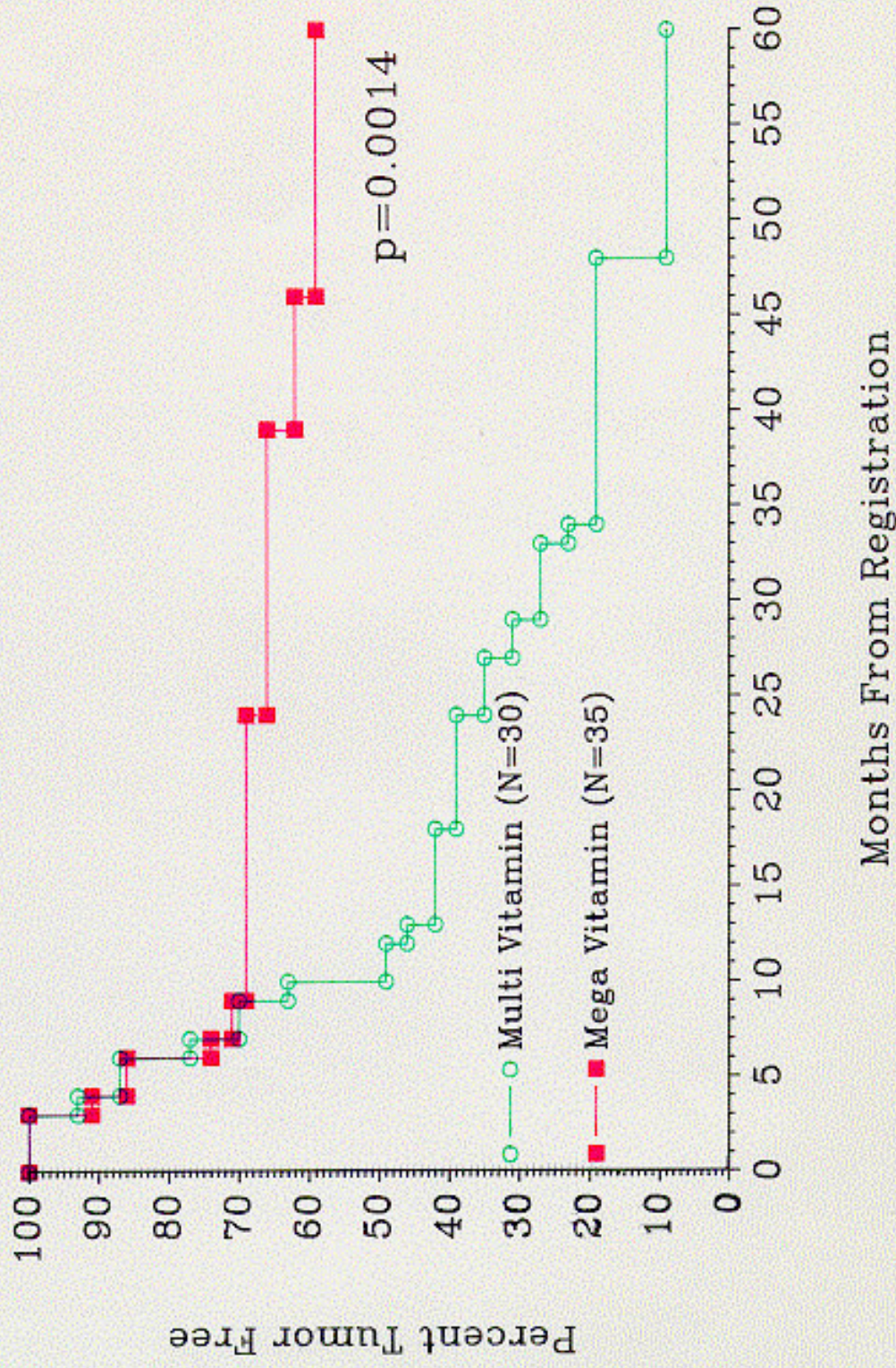
Vitamin E Animal Studies

- 30-60% reduction in carcinogenesis in vivo
- Variable reduction in skin, stomach, colon and breast cancer
- Inhibition of carcinogenesis relates in some studies to dietary fat and selenium intake

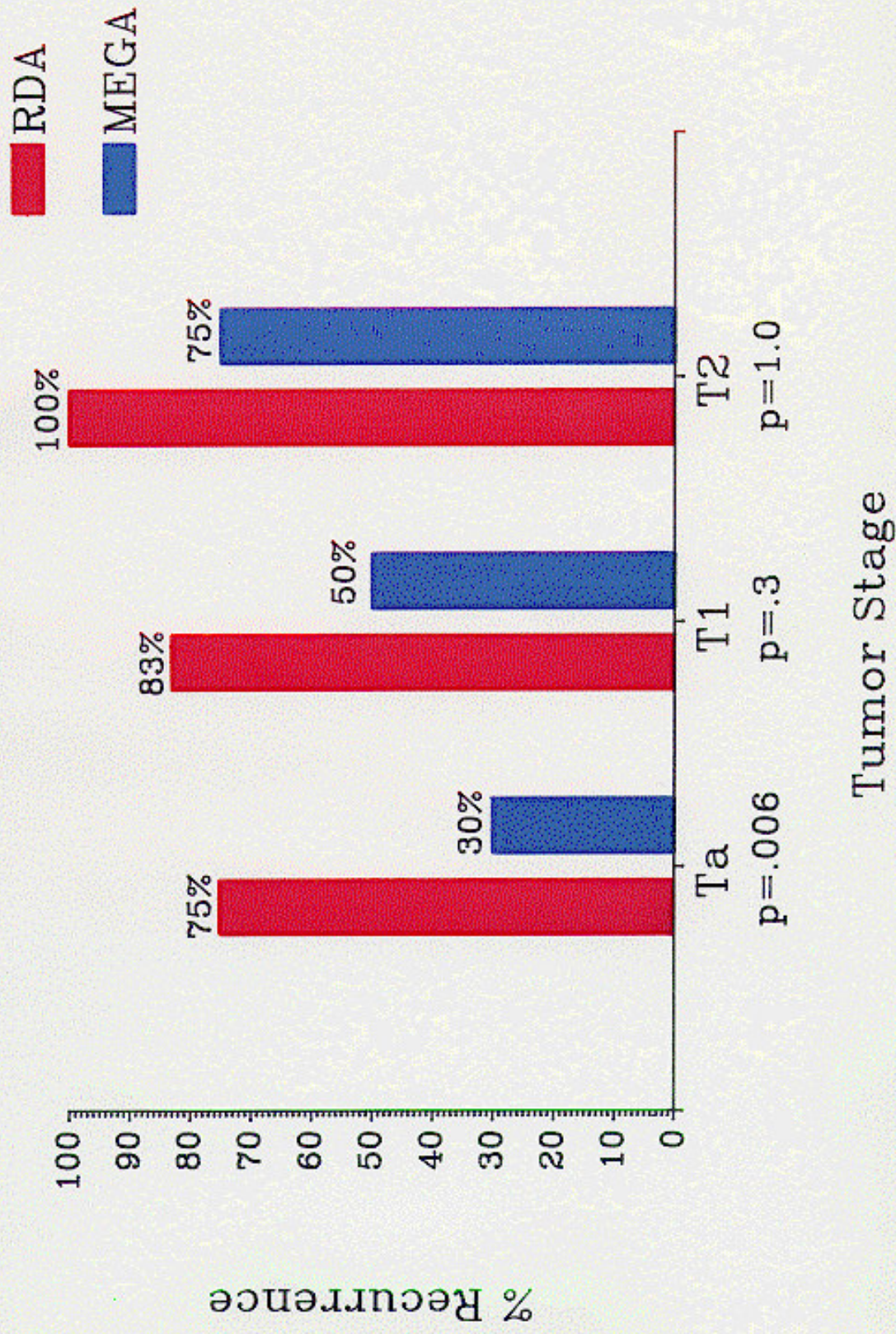
Combination Vitamins (Oncovite) in Bladder Cancer

- **65 patients post bladder tumor resection randomized to RDA vitamins vs high dose:**
 - **40,000 IU Vitamin A**
 - **100mg Vitamin B6**
 - **2,000mg Vitamin C**
 - **400 IU Vitamin E plus 90 mg Zinc**
- **Tumor recurrence reduced from 91% RDA to 41% at 5 years with Oncovite**

Kaplan Meier Estimate of 5 Year Tumor Free Rate In Patients Receiving Vitamin Supplement and BCG Therapy For Bladder Carcinoma

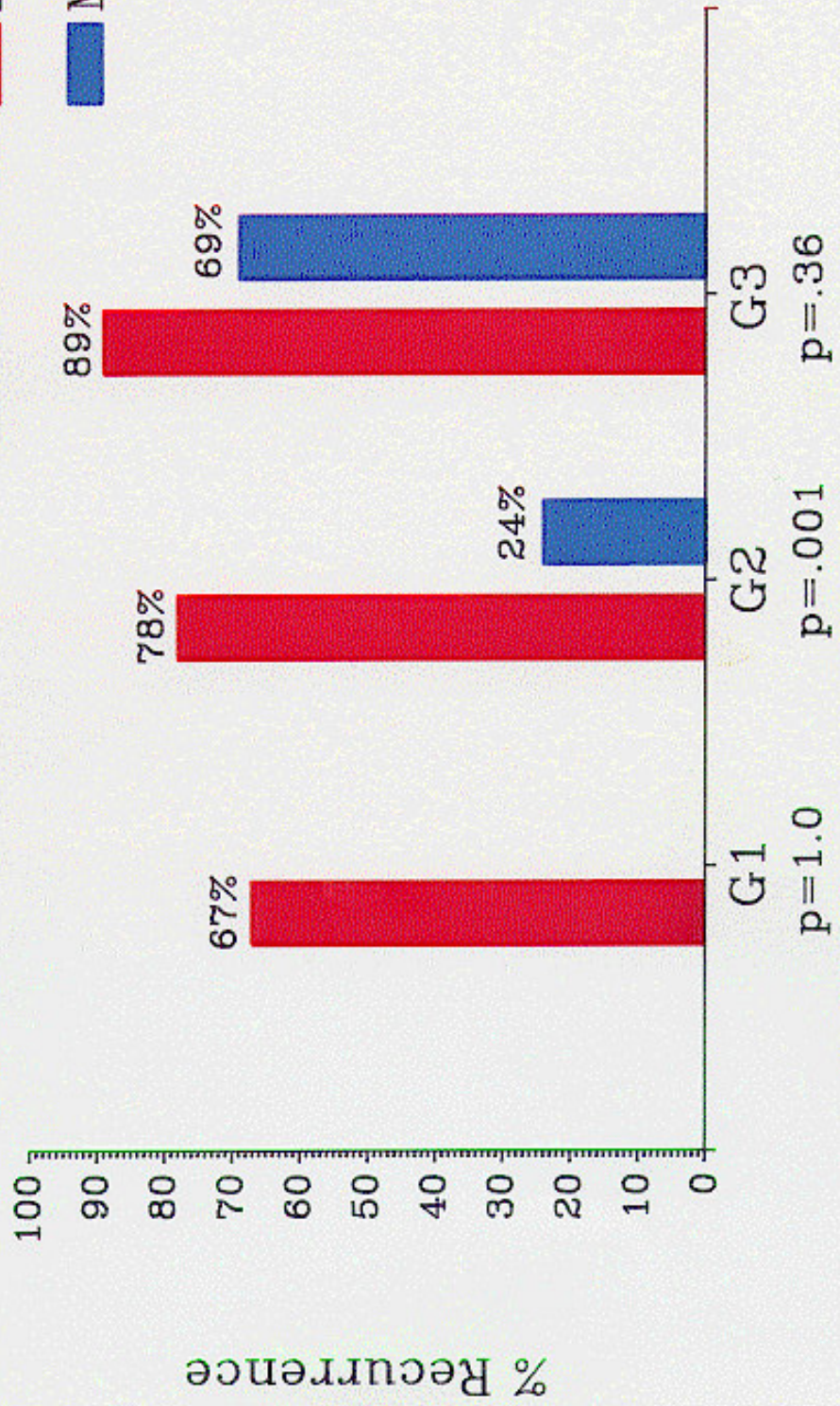


Tumor Recurrence of Patients Receiving Vitamin Supplementation for Bladder Cancer



Tumor Recurrence of Patients Receiving Vitamin Supplementation for Bladder Cancer

RDA
MEGA



Tumor Grade

Oncovite (Vitamins A, B6, C & E) in Bladder Cancer

- Overall recurrence reduced from 80% to 40% (P=0.0011)
- 42% reduction in recurrence in Ta, T1 TCC
- 53% reduction in low grade (G1, G2) TCC
- Associated with statistically significant increase in long-term NK cell activity in BCG treated patients

Chemoprevention Approaches

- Garlic: antitumor activity noted in many tumor models and intralesional, intravesical, or oral administration reduces growth of murine bladder cancer
- Selenium: serum Se levels are lower in pts with bladder ($P=0.03$), prostate and GI cancer vs controls. Se given to reduce skin cancer lowered prostate cancer

Allium sativum (Garlic)

- Ancient herbal remedy, used orally and topically by Egyptians in 1550 BC to treat tumors
- Weisberger & Pensky: 0 vs 100% deaths in AS-treated mice with sarcoma 180 ascites tumor (Science, 126:1112, 1957)
- Animal data: mammary, liver, colon, esophagus and skin carcinoma
- Reduced risk gastric Ca: 40/100,000 vs 3.5

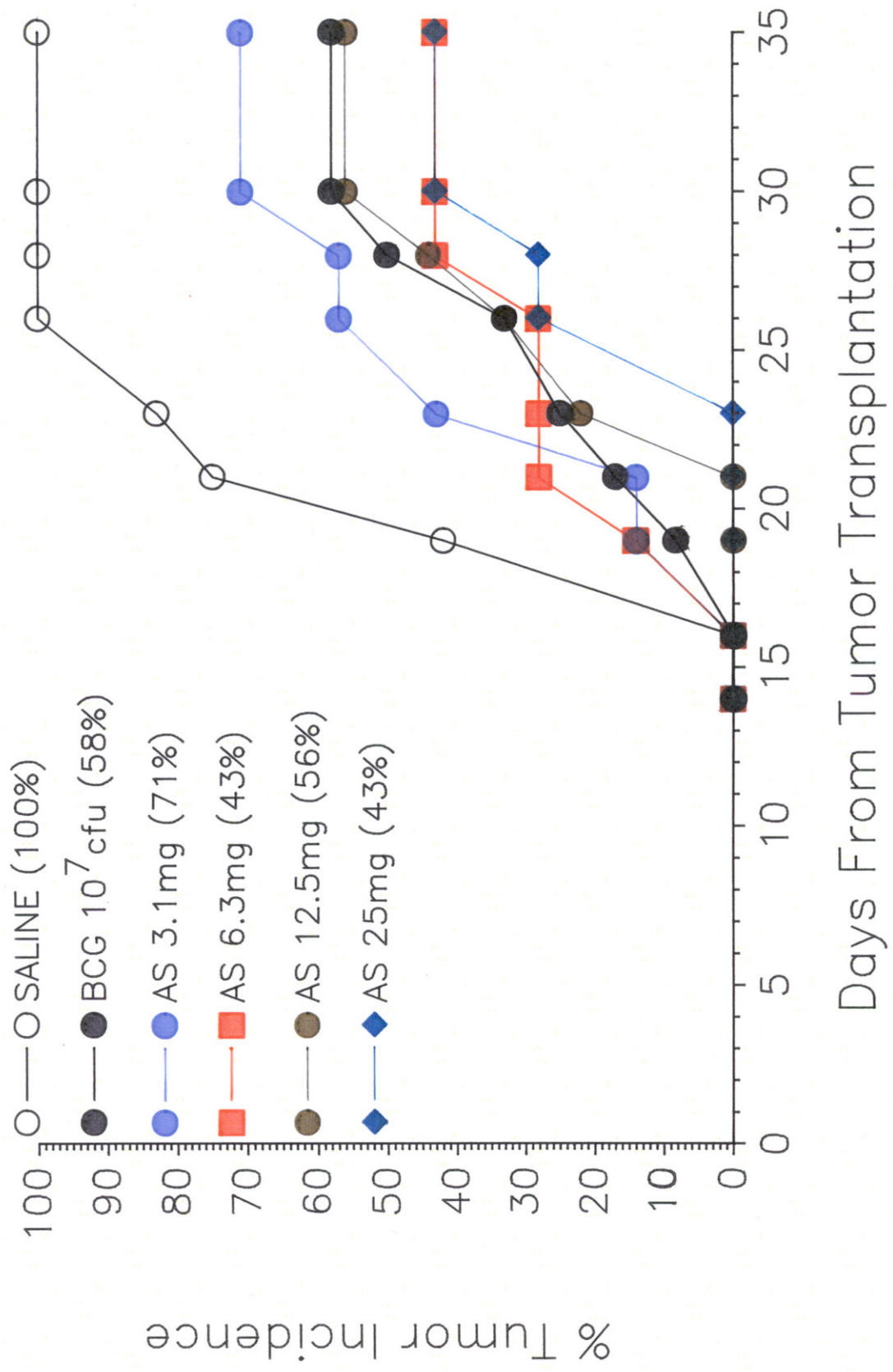
Garlic Mechanisms of Action

- Reduction in N-nitroso compounds (Mie ANS'82)
- Stimulation of glutathione-S-transferase (Sparins et al. Nutr. Cancer, 8:211, 1986)
- Suppress AFB1 induced mutagenesis (Tadi'91)
- Detoxification of heavy metals and toxins
- Free-radical scavenger and source of Selenium
- Enhanced macrophage, T cell and NK activity

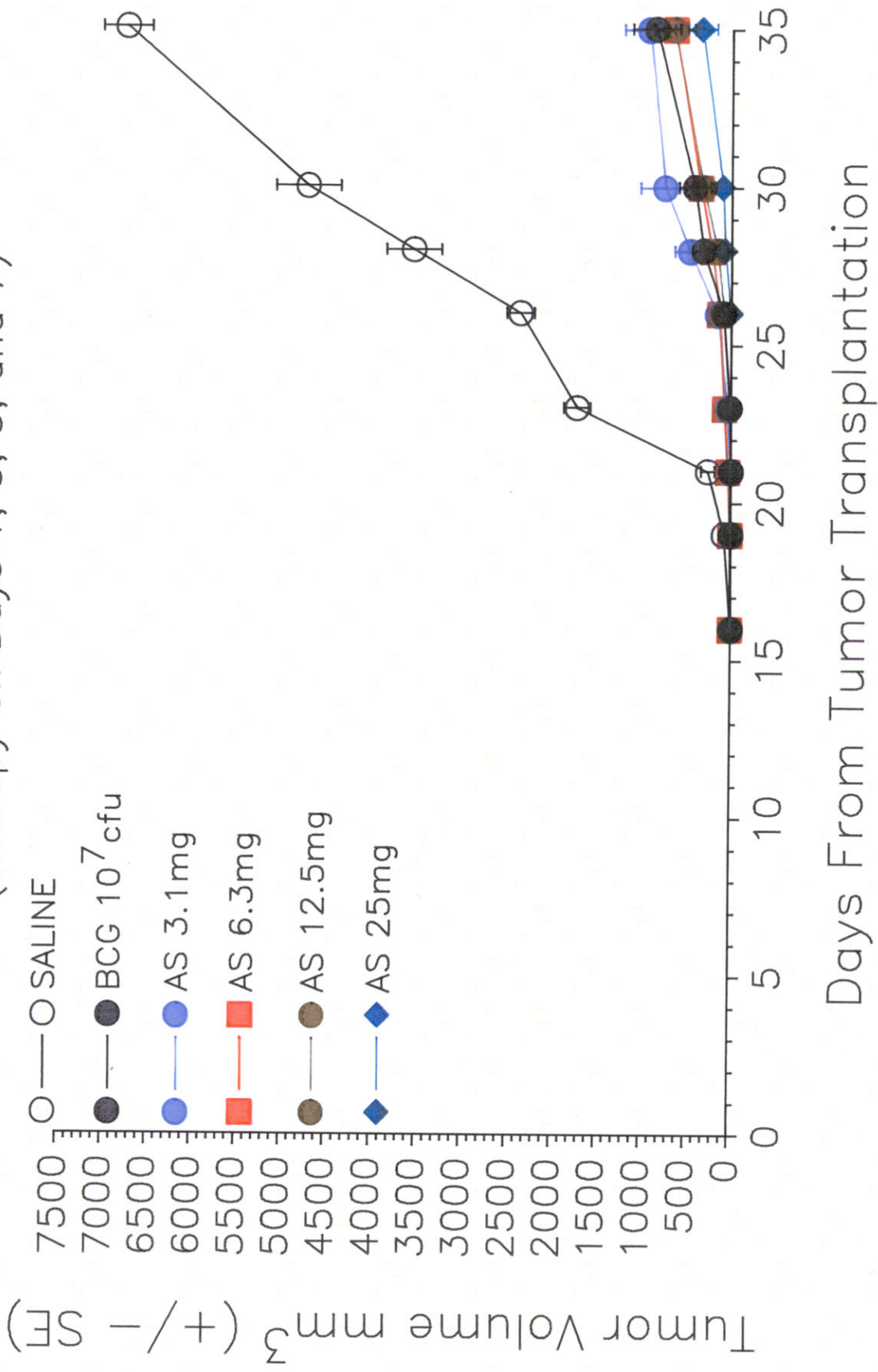
Garlic in Bladder Cancer

- Lau et al. Found intralesional, intravesical and intraperitoneal garlic extract to be as effective as BCG and *C. parvum* in MBT2 murine bladder cancer (J Urol. 136, 1986)
- Associated with macrophage, neutrophil and lymphocyte infiltration in the bladder, splenic hypertrophy, and increased NK and macrophage activity (J Urol. 137, 1987)

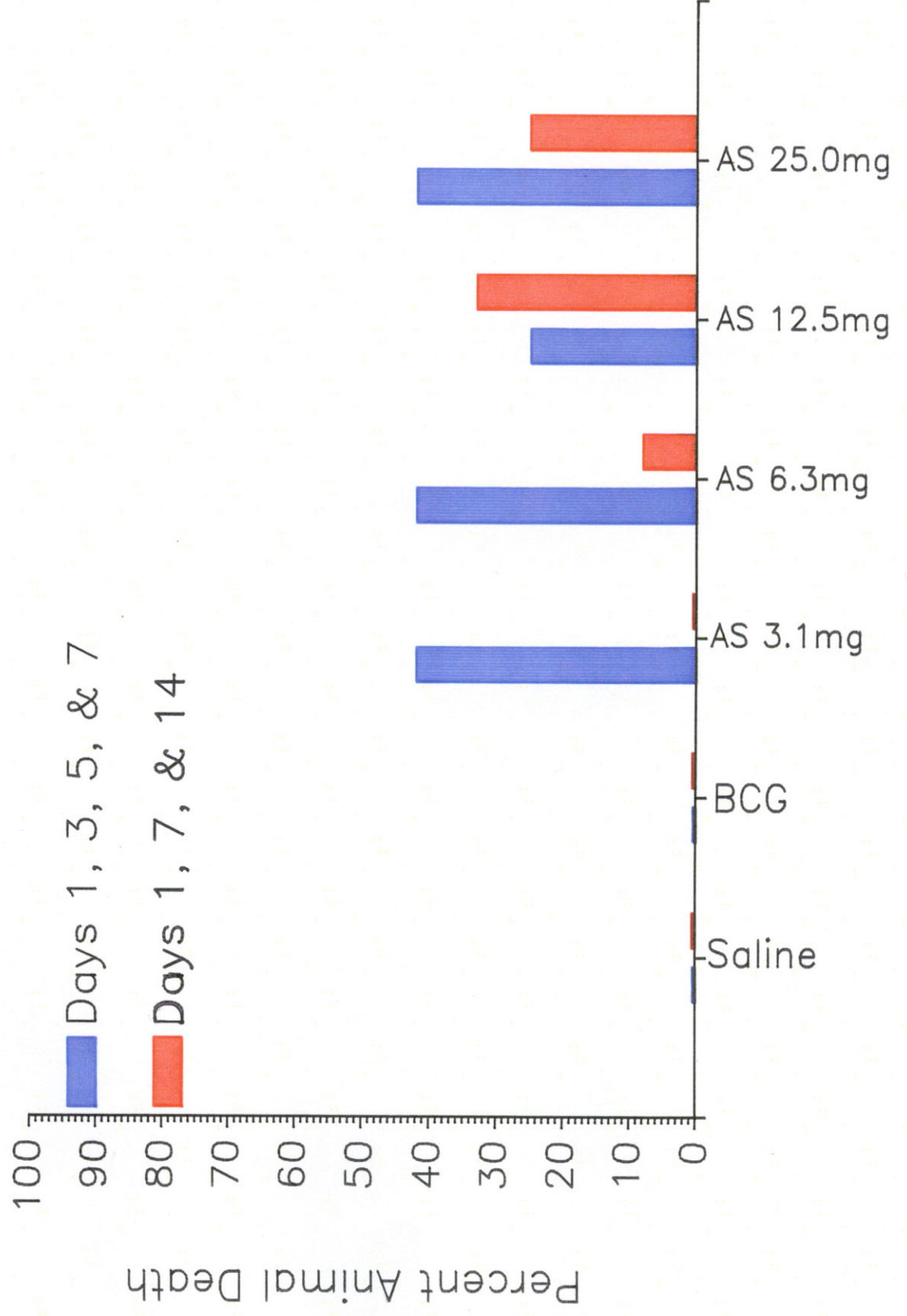
Immunotherapy of Murine Transitional Cell Carcinoma of The Bladder Using Aged Garlic Extract (Therapy on Days 1, 3, 5, and 7)



Immunotherapy of Murine Transitional Cell Carcinoma of The Bladder Using Aged Garlic Extract (Therapy on Days 1, 3, 5, and 7)



Animal Deaths Due to Hypersensitivity Associated with Aged Garlic Extract Immunotherapy



Intralesional AS in Murine TCC

Group	Tumor Inc.	Treat.	Death	Tumor vol.
Saline	11/12 (92%)	0/12		6744mm
BCG	3/12 (25%)*	0/12		860mm**
AS 25mg	2/7 (29%)*	5/12 (52%)		338mm**
AS 12.5mg	4/9 (44%)*	3/12 (25%)		658mm**
AS 6.3mg	2/7 (29%)*	5/12 (42%)		639mm**
AS 3.1mg	4/7 (57%)	5/12 (42%)		941mm.**

*P<0.05

**P<0.001

In Vitro Cytotoxicity of Aged Garlic Extract (MTT Assay)

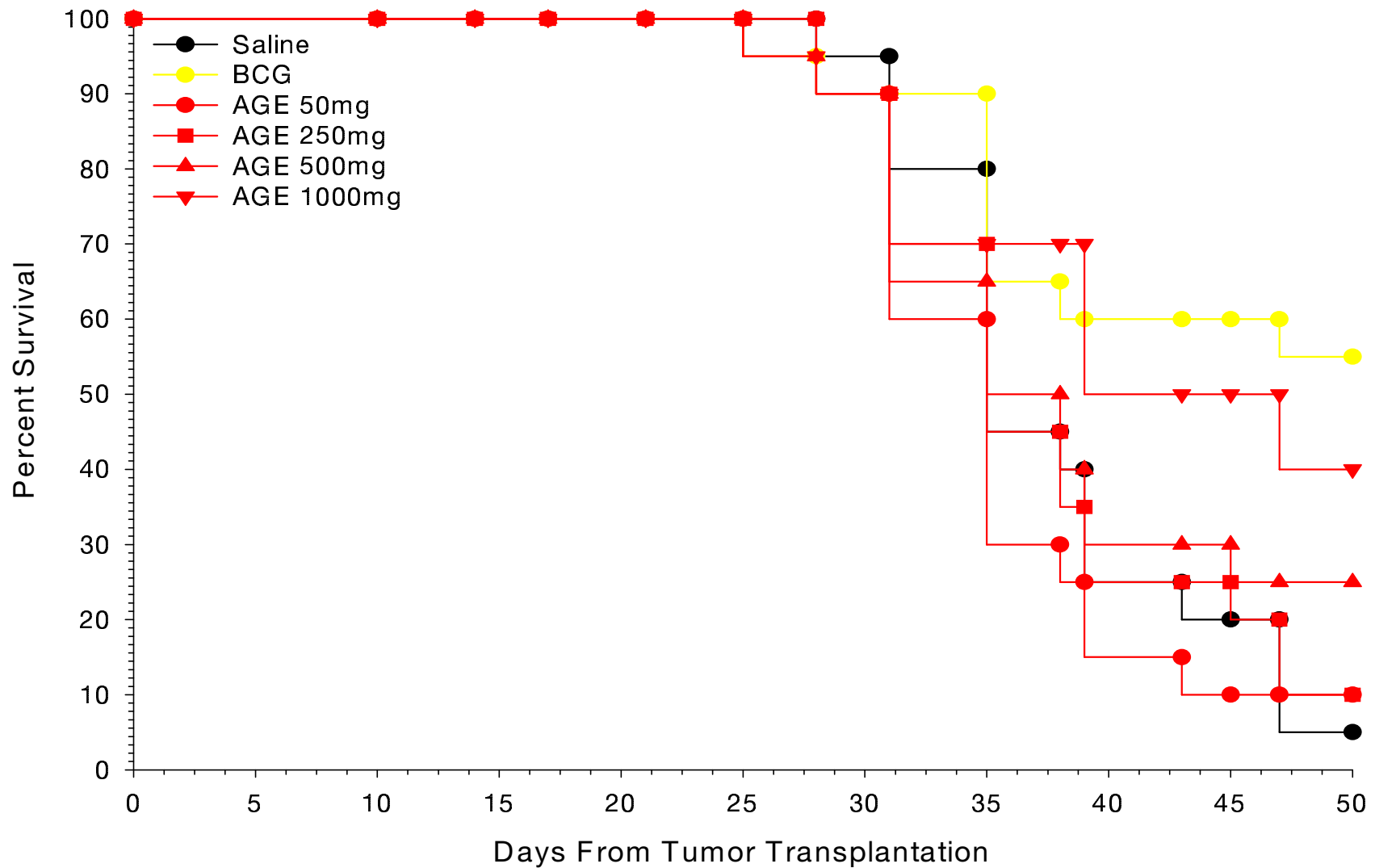
Drug Concentration	% Cell Cytotoxicity
Control	0
AGE 250mg/ml	98.5%
AGE 125mg/ml	98.5%
AGE 62.5mg/ml	29.9%
AGE 31.3mg/ml	13.5%
AGE 15.6mg/ml	0
AGE 7.8mg/ml	-9%
AGE 3.9mg/ml	0.4%

Orally Administered Garlic in Transplanted Murine TCC (MBT2)

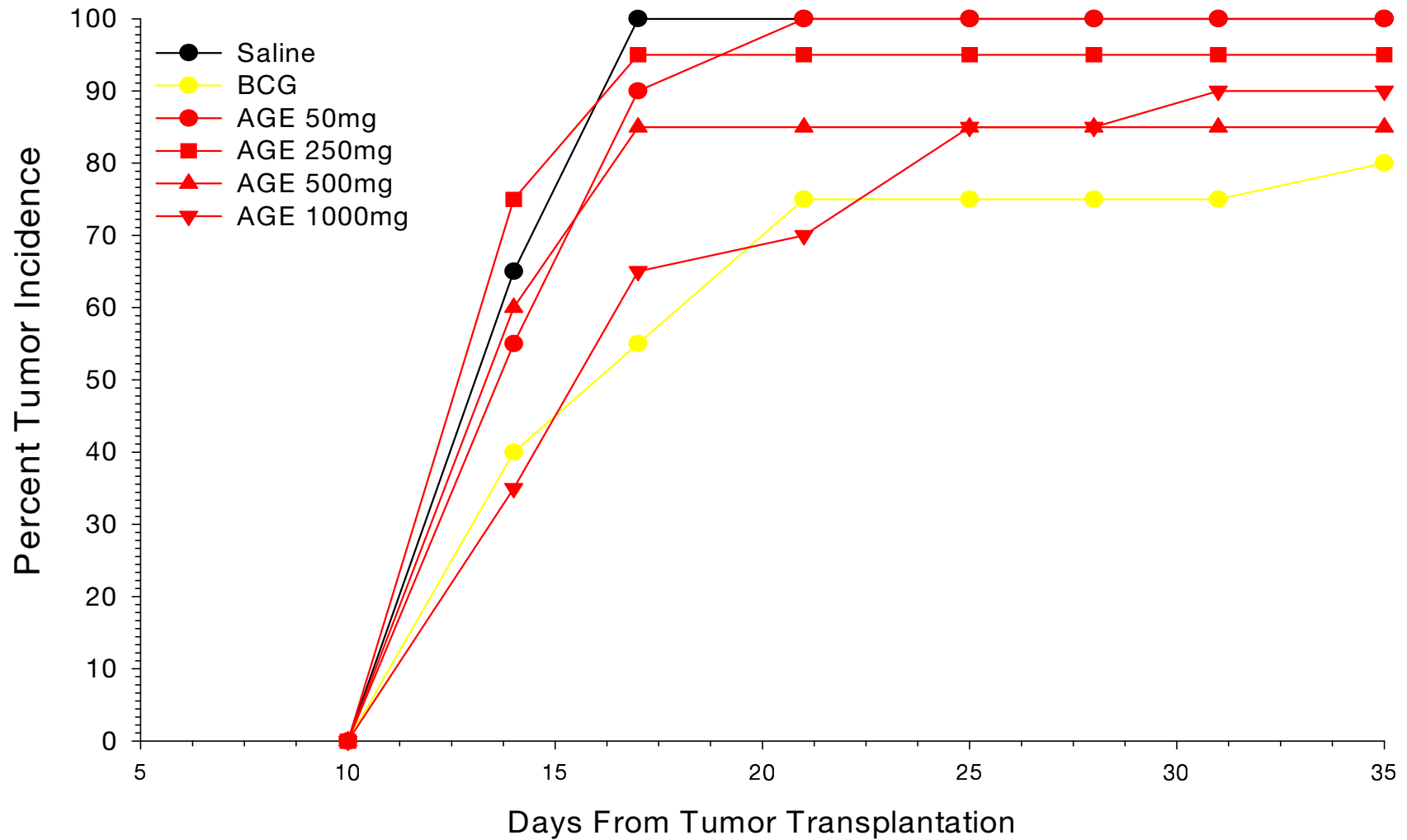
Group	Tumor Inc. Volume	Survival
Saline	18/20 (90%)	4047 20%
BCG	3/20 (15%)*	390* 75%*
AS 5mg	17/20 (85%)	4670 15%
AS 50mg	14/20 (70%)	2563** 40%
AS 500mg	12/20 (60%)**	1644* 50%**

*P<0.001; **P<0.05

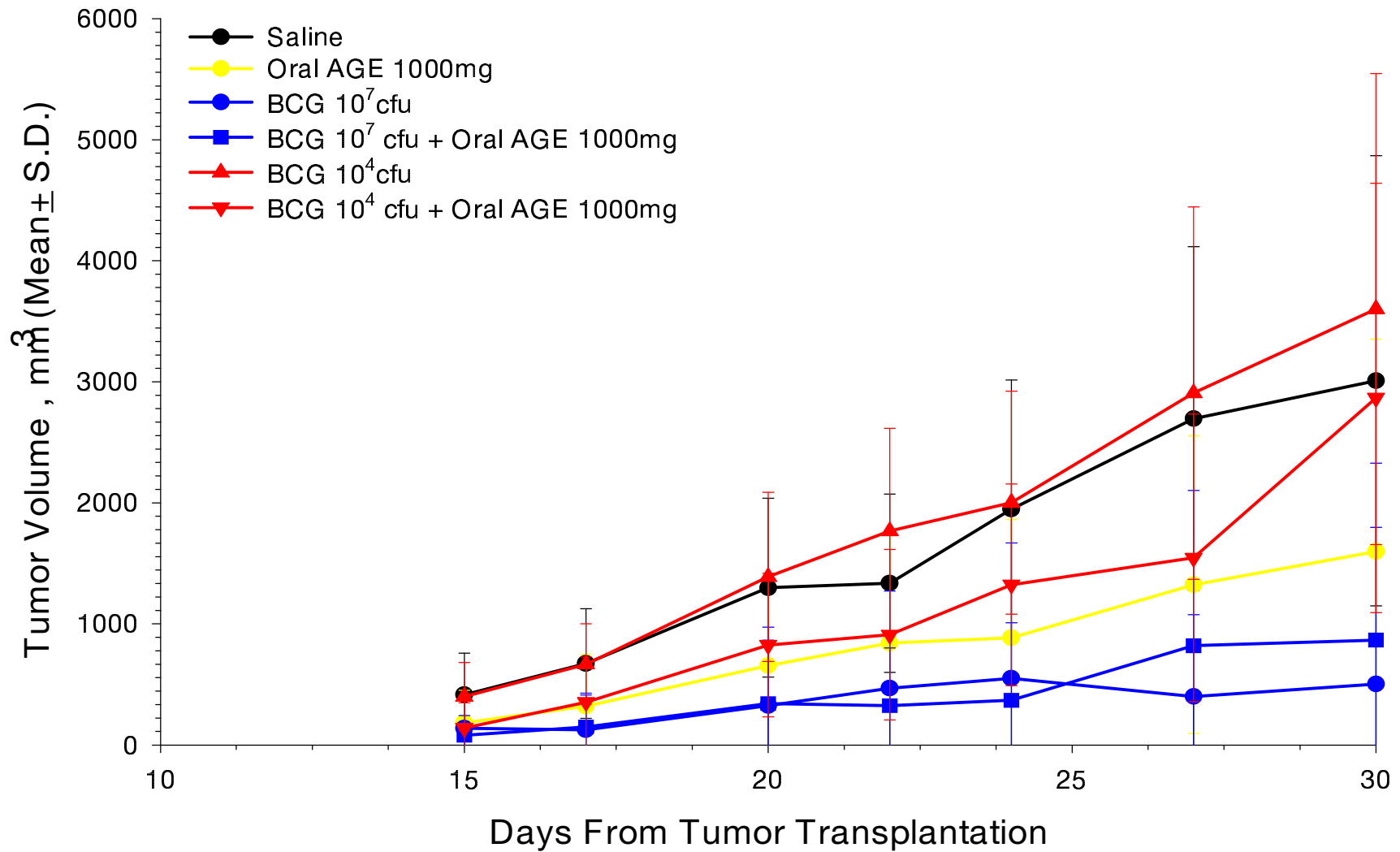
Effects of Orally Administered Aged Garlic Extract (AGE) in the MBT2 Murine Bladder Cancer Model



Effects of Orally Administered Aged Garlic Extract (AGE) in the MBT2 Murine Bladder Cancer Model



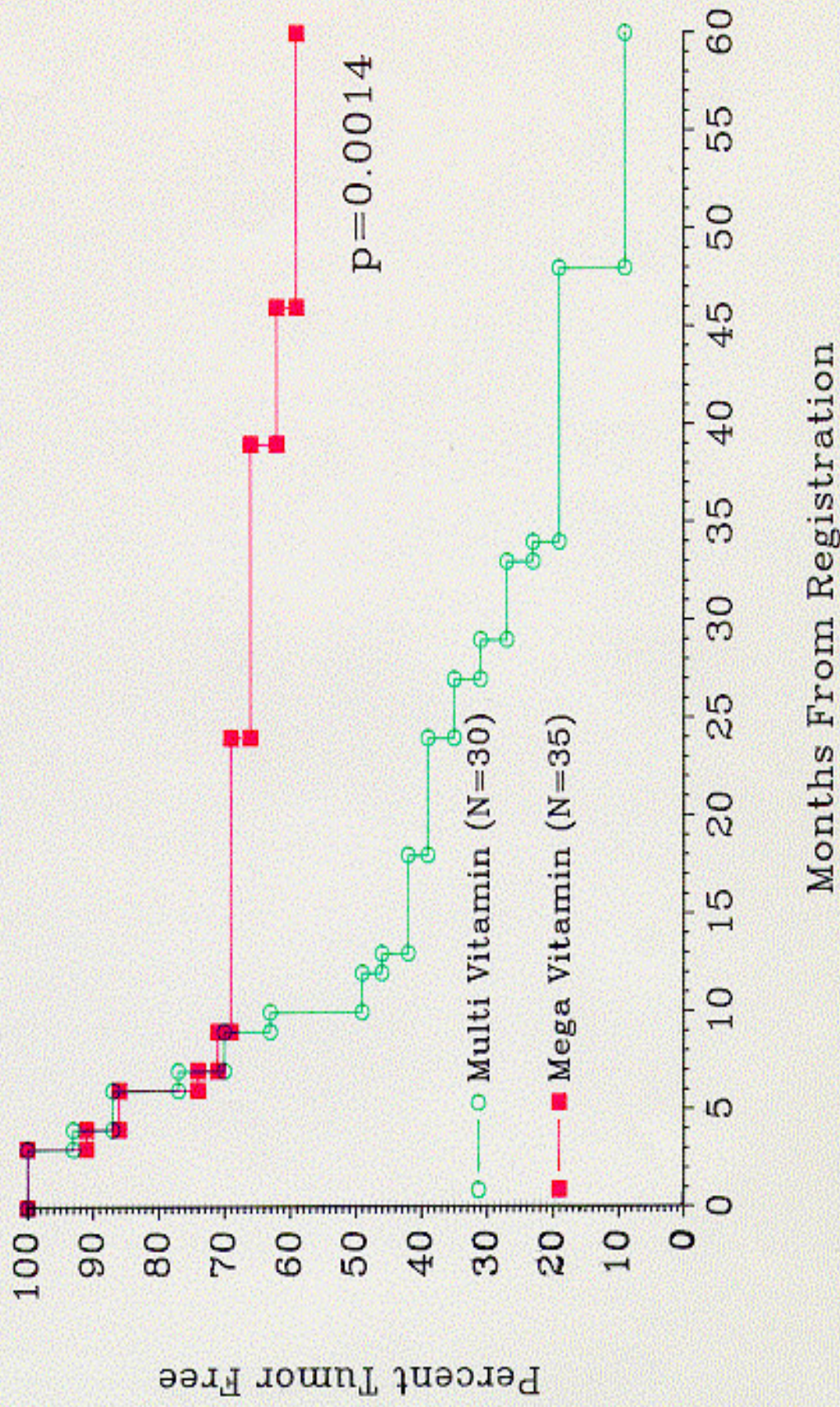
Effects of Orally Administered Aged Garlic Extract (AGE) in the MBT2 Murine Bladder Cancer Model



Chemoprevention Approaches

- Difluoromethylornithine (DFMO) inhibits polyamine synthesis and reduces nitrosamine-induced murine bladder cancer; clinical trials showed no effect (Lerner, AUA, 2005).
- NSAIDS: ketoprofen, sulindac and piroxicam have strong chemopreventive effects; 17% response in canine bladder cancer

Kaplan Meier Estimate of 5 Year Tumor Free In Patients Receiving Vitamin Supplement and BCG Thera For Bladder Carcinoma



Conclusions and Recommendations

- Our Western diet, high in animal fat and protein, is carcinogenic as well as atherogenic
- Unfortunately, our Western diet is spreading to the East, increasing the incidence of cancer there
- Current recommendations for vitamin intake may be suboptimal
- Based on epidemiologic, biochemical, in vitro, animal model and clinical studies, vitamins could be recommended as an appropriate supplement to standard treatment in many cancer patients

Conclusions and Recommendations

- Based on our double-blind study showing 50% reduction in 5yr bladder tumor recurrence, we now recommend in TCC:
 - 32,000 IU Vitamin A
 - 100mg Vitamin B6
 - 2,000mg Vitamin C
 - 400-800 IU Vitamin E
- And based on other studies we include:
 - Vitamin D 1600 IU and Folic Acid 1.6mg

Conclusions and Recommendations

- Based on our double-blind study showing 40% reduction in 5yr bladder tumor recurrence, we now recommend in TCC:
 - 32,000 IU Vitamin A
 - 100mg Vitamin B6
 - 2,000mg Vitamin C
 - 400-800 IU Vitamin E
- And based on other studies we include:
 - Vitamin D 1600 IU and Folic Acid 1.6mg



“Oncovite”

Conclusions

- Garlic, as well as many other ancient herbal remedies, could have a major impact on cancer prevention and treatment
- Studies should be done to determine the efficacy of garlic preparations, Oltipraz, *vitamins, *NSAIDS, *DMFO, and other natural and synthetic agents.

* Studies currently in progress

Bladder Cancer, with its high recurrence rate, accessibility, and exposure to both the blood and the urine stream, is an excellent tumor system for the evaluation of chemopreventive agents

New Cancers After BCG

Cancer Site	BCG 6	BCG 27	Total
Prostate	14	5	19
Lung	11	7	18
Colorectal	4	6	10
Other	11	4	14
Unknown	6	2	8
Total:	46 (23%)	24 (13%)	70

P=0.014

Reduction in Prostate Cancer

	Induction	BCG Maint.
Stage A:	1	0
Stage B:	3	2
Stage C:	3	1
Stage D:	3	0
Unknown:	4	2
Total:	14 (6.9%)	5 (3.3%)

P=0.04

Prostate Cancer Chemoprevention

- Hormonal agents: finasteride, dutasteride
- NSAIDS: aspirin, ibuprophen, COX-2
- Vitamins: E, D, A, C?
- Antioxidants: lycopene, resveratrol
- Nutrients: cruciferous veg, pomogranites?
- Phytoestrogens: genistein,
- Statins?

5 alpha Reductase Inhibition

- Finasteride reduced prostate cancer by 24.8%, but increased high grade (8-10) cancers from 5.0% to 11.9%
- Calculated person-years saved with finasteride: 316,700; reduced to 262,567 if 6.9% increase in high grade cancers is real

Unger, JM: Cancer. April, 2005

NSAIDS

- PSA reduction has been reported with COX-2 inhibitors
- Review/meta-analysis of 91 epidemiologic studies show significant decline in risk of 4 major cancers with increased intake of NSAIDS, primarily aspirin and ibuprofen:
Colon: 63% Prostate: 39%
Lung: 36% Breast: 39%

Harris RE: Oncol Rep. April, 2005

Vitamins

- Vitamin D: CAP inversely related to sunshine; D3 derivative plus taxotere prolonged survival 7+ mo v tax alone
- Vitamin E: significant reduction CAP in skin cancer prevention trial. 32% drop in ATBC study. 32,000 pts under study
- CK3: 8/10 HRPC patients with reduced PSA slope. My pt: 10,000+ PSA drop

Combination Vitamins C, E, beta carotene, Se and Zn

- 5141 randomized men in Canadian trial
- Statistically insignificant 12% reduction in CAP
- Significant 48% reduction in CAP among men with normal PSA (<3) with combination vitamins/minerals
- Single agent antioxidants may cause an imbalance- antioxidants work in concert

Antioxidants

- Lycopene: HPFS found 35% reduction in CAP with increased intake of tomato products. 8:7 positive/negative studies
- Selenium: 200ug/d associated with 50% reduction in CAP in the NPC trial
- Resveratrol: 4 glasses of red wine/week may reduce CAP 50%, but tea may be better!
(Stanford JL: Int J Ca. Sept. 2004)

Statins

- Statin use is associated with a reduced risk of prostate cancer
- In a prospective study over 9 years, statins reduced PSA 42% while the untreated controls had a 38% increase (J Urol. 173:1923, 2005)
- Statins have antiproliferative activity and induce apoptosis in vitro and in vivo

Conclusions

- It is better to prevent than treat
- Our Western diet promotes atherosclerosis and cancer
- Cost and toxicity of agents are not necessarily proportional to efficacy
- Lifestyle and diet changes can impact duration and quality of survival
- ***Combination*** Prevention Pills, like chemo, hormone and immune therapy, are best: there is no silver bullet!

BCG Maintenance: Not Created Equal

