Updates on the Role of Nutrition Support in Cancer

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Learning Objectives

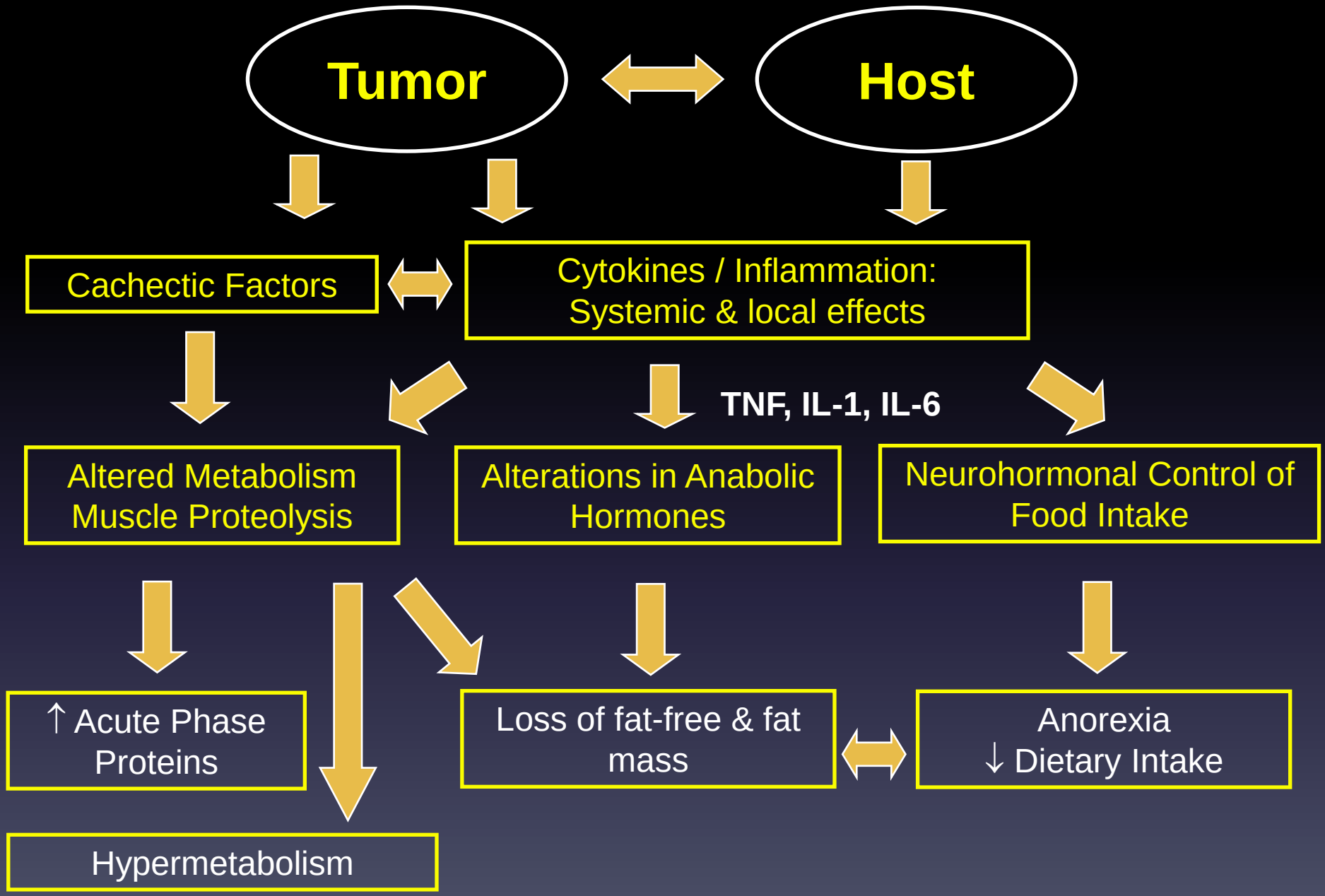
After this presentation, attendees will be able to:

1. Identify new evidence on the role of starvation in chemotherapy
2. Discuss published evidence supporting tumor growth with nutrition support
3. Evaluate the role of medical marijuana in the cancer patient

Nutrition in Cancer

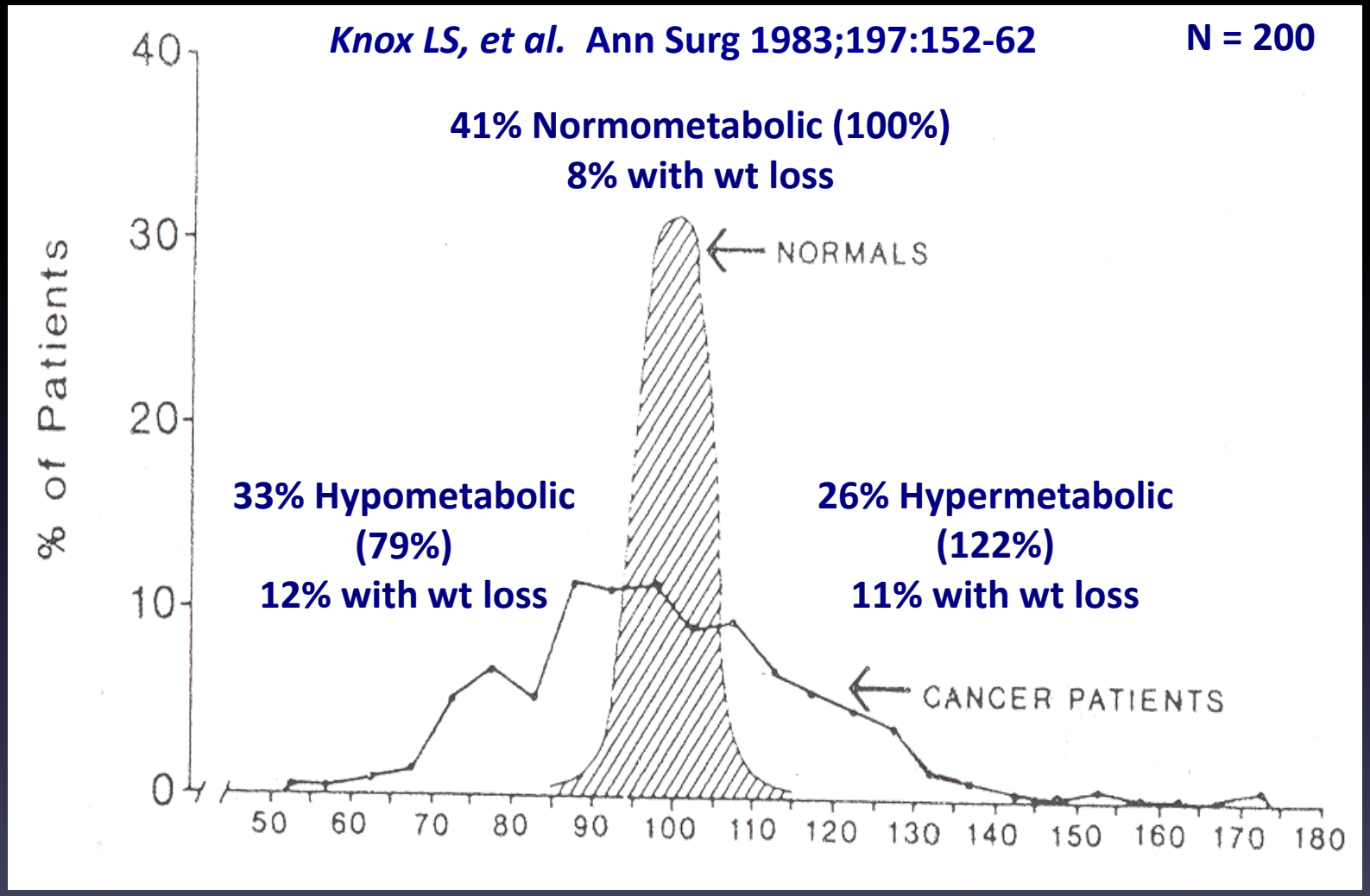
- Among 21 NCCN institutions surveyed, only four (19%) provided dietary recommendations for patients undergoing cancer treatment.
  - Another five institutions (24%) referenced external websites for such information.
  - Among the nine external websites referenced by NCCN institutions for dietary information, only four (44%) provided recommendations specifically for patients during or following cancer treatment.
- Of the four NCCN institutions that provided recommendations on their websites, two recommended diets containing equivalent proportions of carbohydrate-rich, protein-rich, and fat-rich foods.
  - The other two recommended diets consisting primarily of carbohydrate-rich foods.
  - The dietary information on websites referenced by the NCCN institutions, which included the NCI website and those of the American Cancer Society and the American Society of Clinical Oncology, also lacked consistency, the researchers found.

Champ CE, et al. **Nutr Cancer 2013;65:430-9**



Strasser F. **Supp Care Cancer 2003;11:11-20**

Energy Expenditure in Cancer



41% of advanced solid cancer patients with 9% weight loss were hypermetabolic

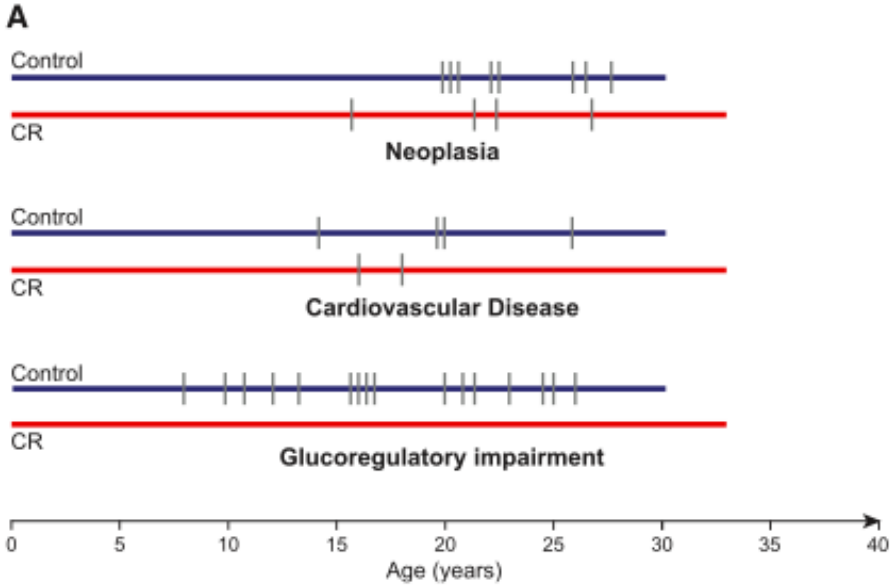
Del Fabbro E, et al. **J Palliat Med 2011;14:1004-8**

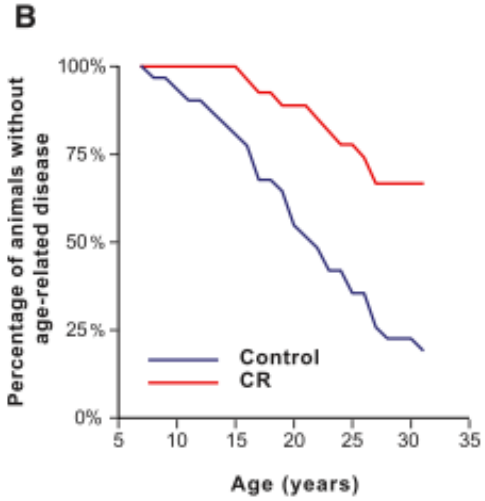
Dietary Restriction

- 20–40% reduction in calorie intake
  - Also refers to more/less severe restrictions or to reduced/lack of daily intake of particular dietary components, including amino acids, protein or fats
  - Promotes stress resistance
    - Downregulates conserved nutrient-signaling proteins, or by activating stress resistance transcription factors negatively regulated by pro-aging pathways

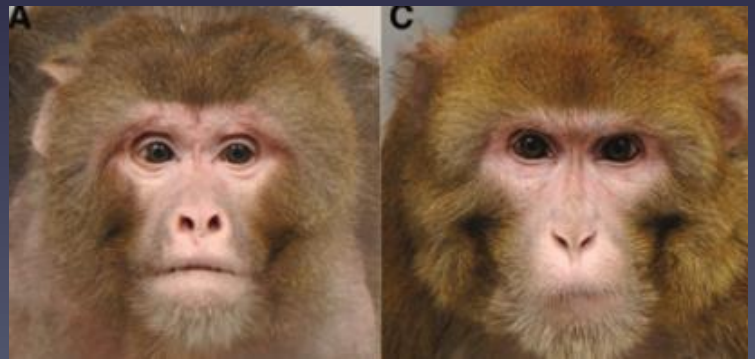
Effects of Dietary Restriction

Fig. 3. Effect of CR on age-associated disease. **(A)** Incidence of three major age-related conditions. Hash marks represent the age of diagnosis. Individual animals with multiple discrete diagnoses are represented multiple times. **(B)** Data represent the first occurrence of any age-related disease in each individual animal.



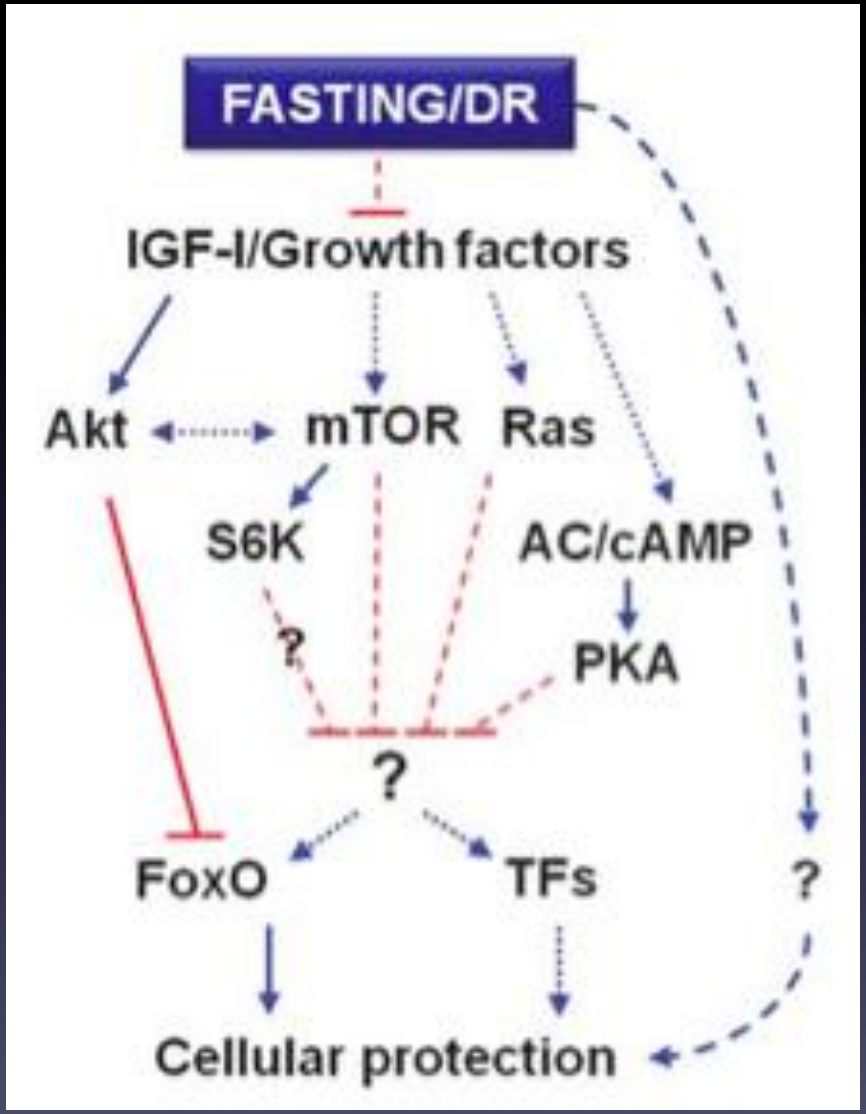


- 37% of the control rhesus monkeys died of age-related causes as compared to only 13% of the Caloric Restriction group



Colman RJ, et al. Science 2009;325:201-4

Dietary Restriction (DR)

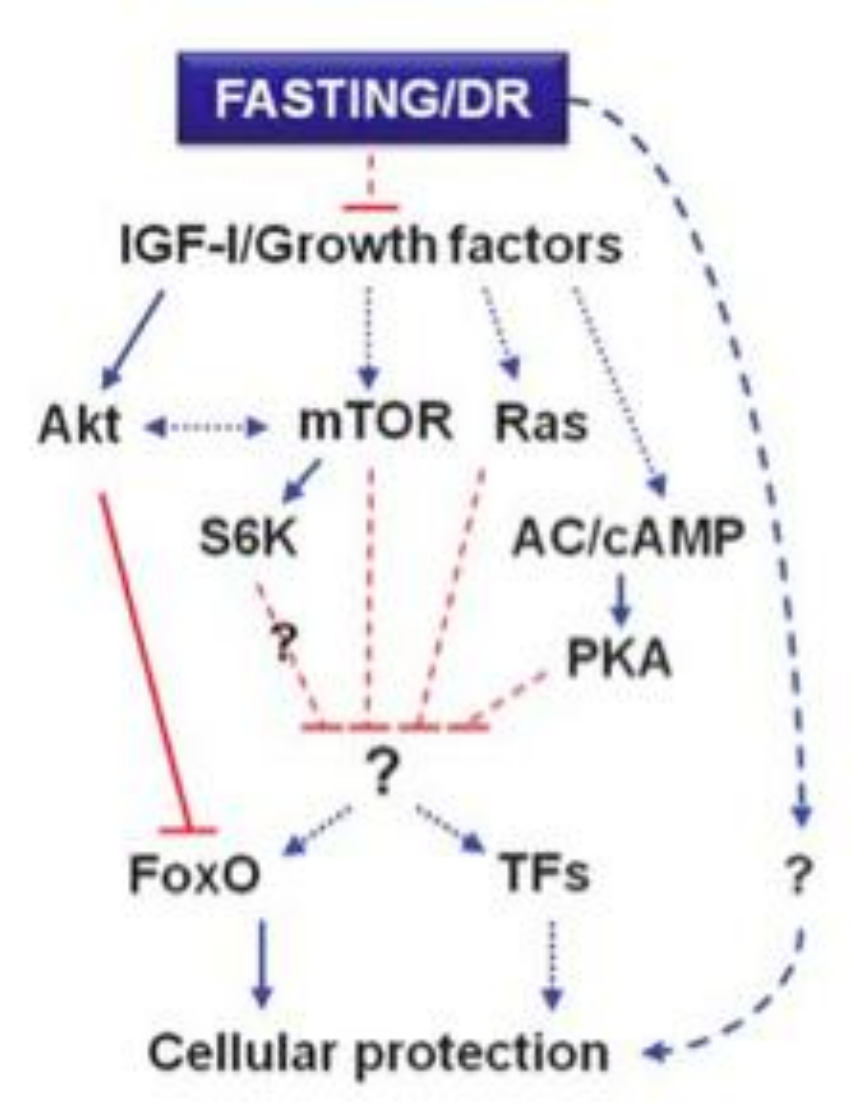


- Connection between cancer & stress resistance provides theoretical basis for differential killing of cancer cells by the activation of stress resistance in normal cells & treatment with chemotherapy

- Differential stress resistance is based on normal cells in response to fasting will enter an alternate state:
  - Reduced / lack of cell division
  - Switch to utilization of metabolites generated from breakdown of fats, proteins and organelles (autophagy)
  - Resistance to multiple stresses

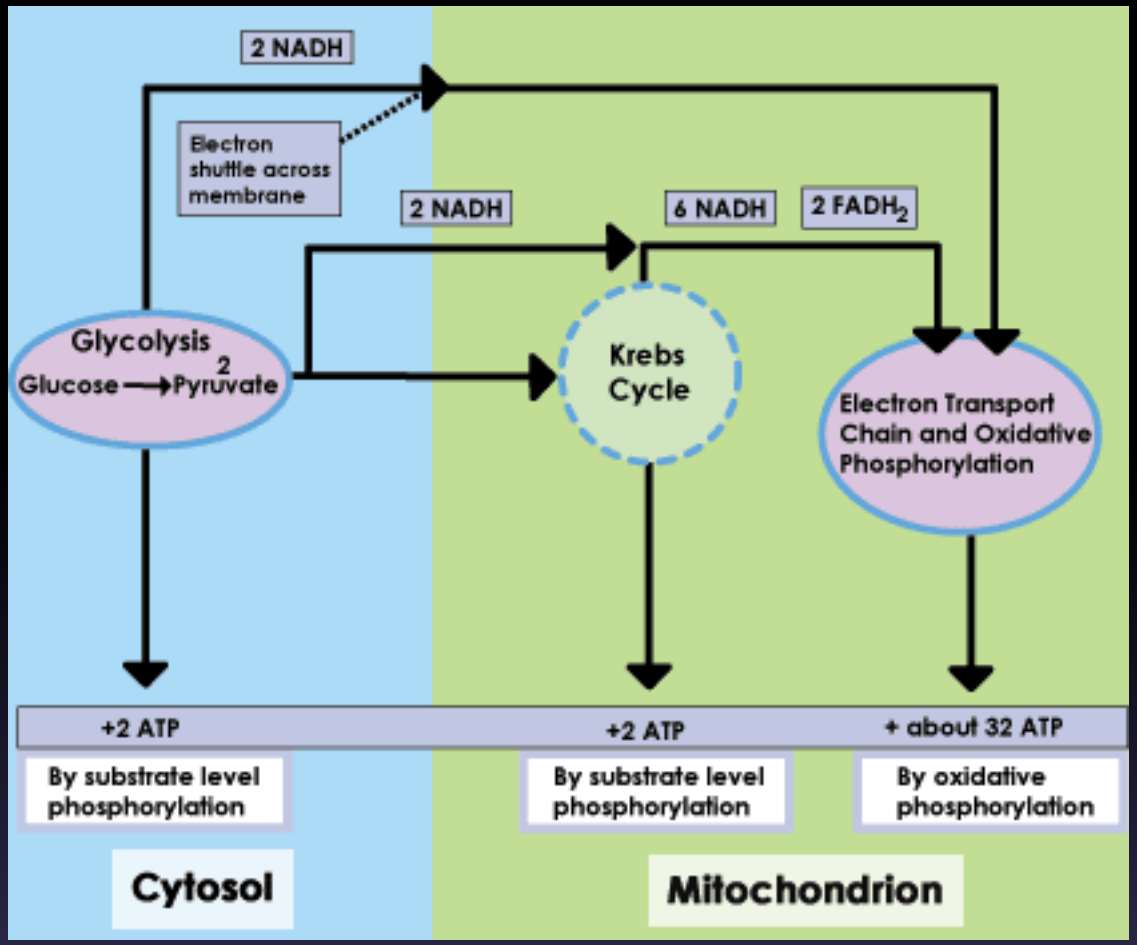
Lee C, et al. **Oncogene 2011;30:3305-16**

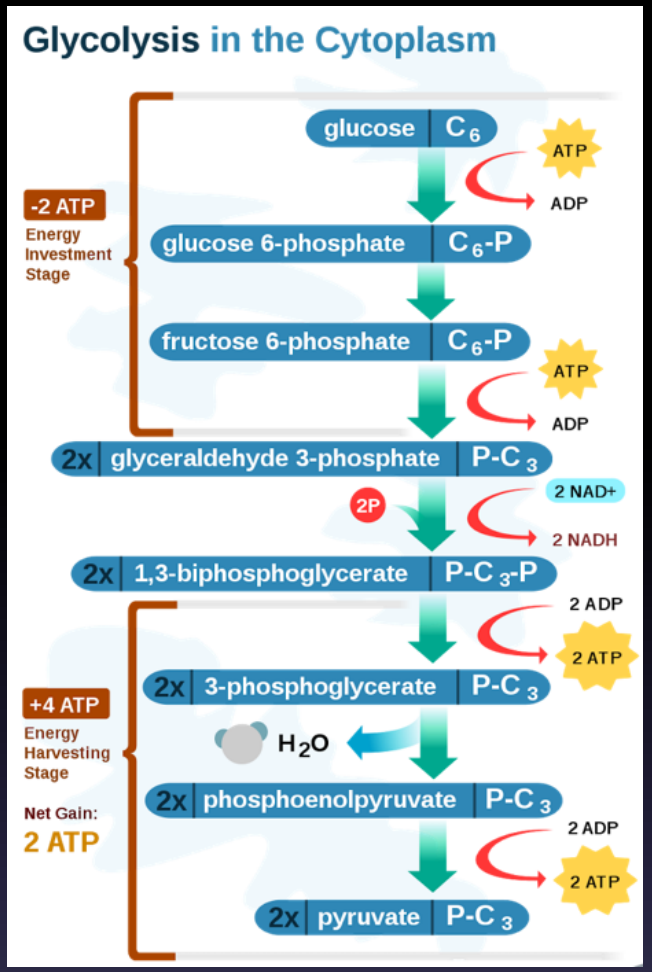
Dietary Restriction (DR)



- Oncogenic mutations that cause hyperactivation of IGF-I, Akt, Ras, mTOR and PKA are among the most common in human cancers
- Specific oncogenes render tumors unresponsive to DR, suggesting the efficacy of a reduction in food intake may be limited to a subset of cancers

Lee C, et al. **Oncogene 2011;30:3305-16**

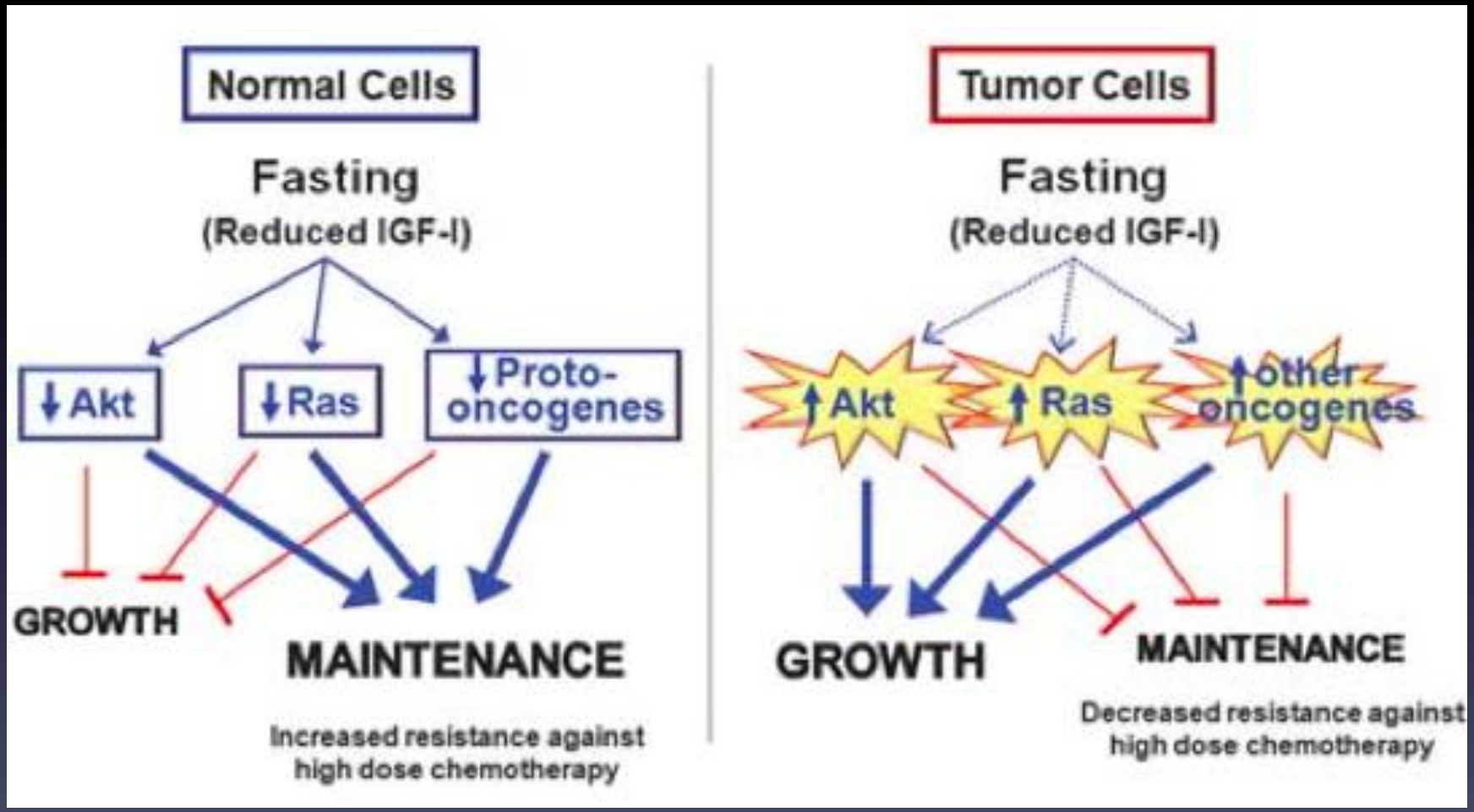




Oxidative phosphorylation is superior to glycolysis in terms of ATP production

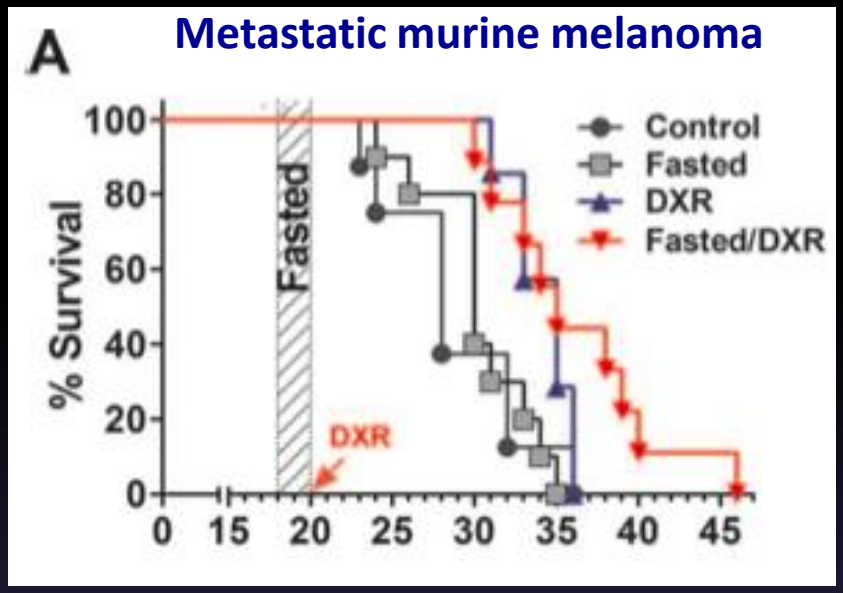
- Glycolysis provides biosynthetic precursors that are essential to rapidly dividing cells
  - Glucose-6-phosphate can be directed to the pentose shunt pathway, providing reducing power and substrate for nucleotide synthesis
  - Glycerol can be processed into phospholipids that contribute to the cell wall
  - Increased glucose metabolism allows cancer cells to restrict apoptosis, further favoring tumor cell survival

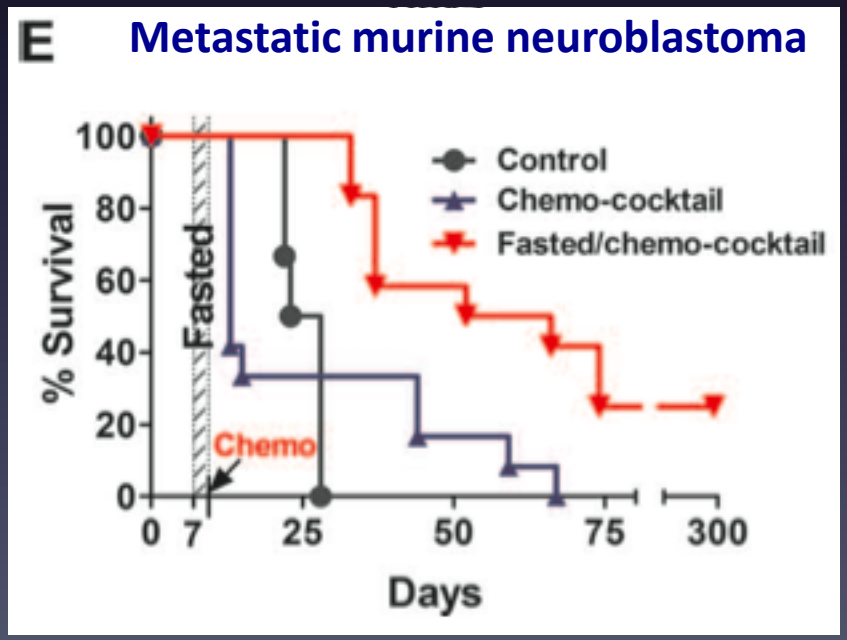
Short-term Fasting

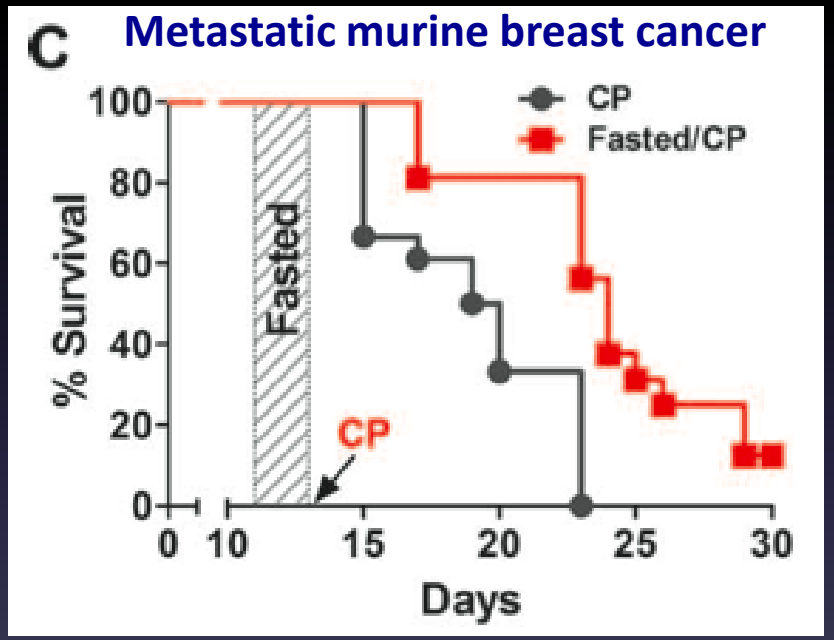


Lee C, et al. **Oncogene 2011;30:3305-16**

48-hour Fasting with Chemotherapy

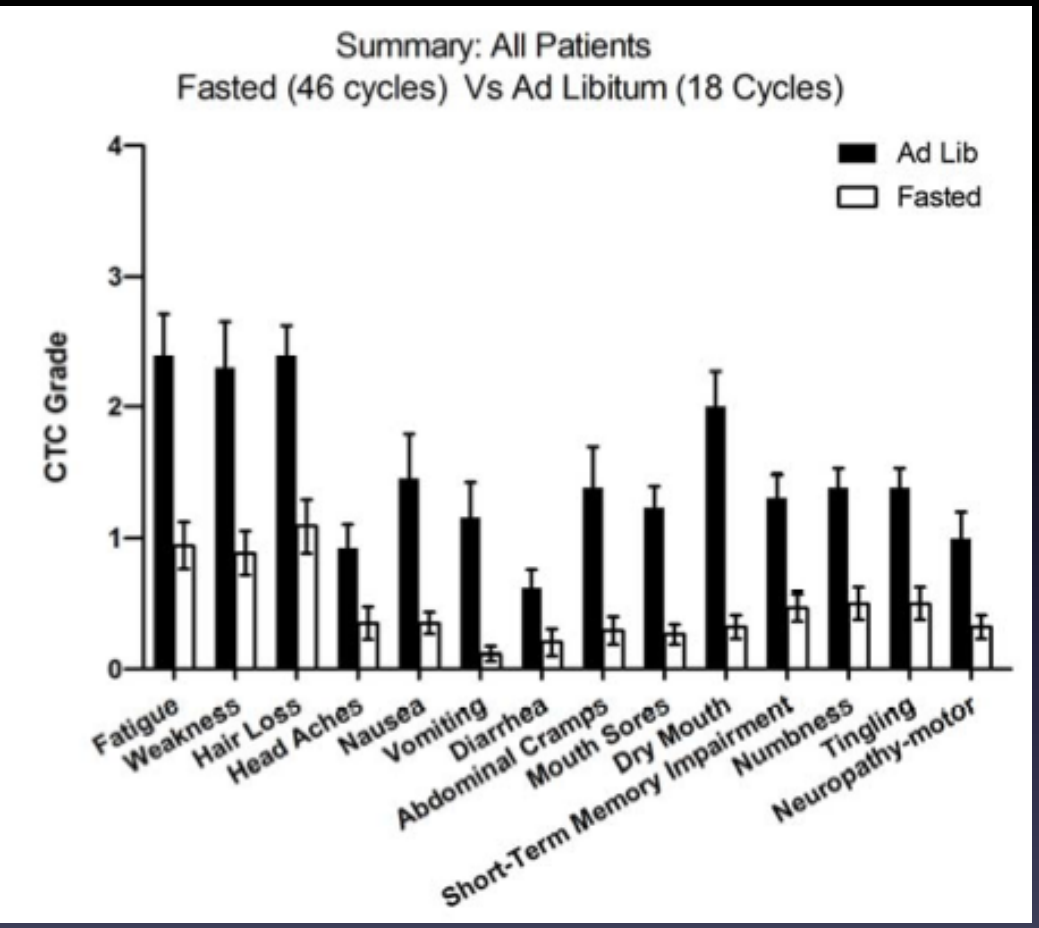






Lee C, et al. Sci Transl Med 2012;4(124):124ra27

Fasting & Chemotherapy in Humans



Common Terminology Criteria for Adverse Events (CTC) of the National Cancer Institute

- 10 patients with a variety of malignancies voluntarily fasted prior to (48-140 hours) and/or following (5-56 hours) chemotherapy
- For patients where cancer progression could be followed, there was no evidence that fasting protected tumors or interfered with chemotherapy efficacy

Safdie FM, et al. **Aging (Albany NY) 2009;1:988-1007**

Targeting Insulin Inhibition with DR

Table 2
Mean daily ingestion of macronutrients* over the duration of the pilot trial

Mean age 62.9 yrs with 5.5 yrs of cancer

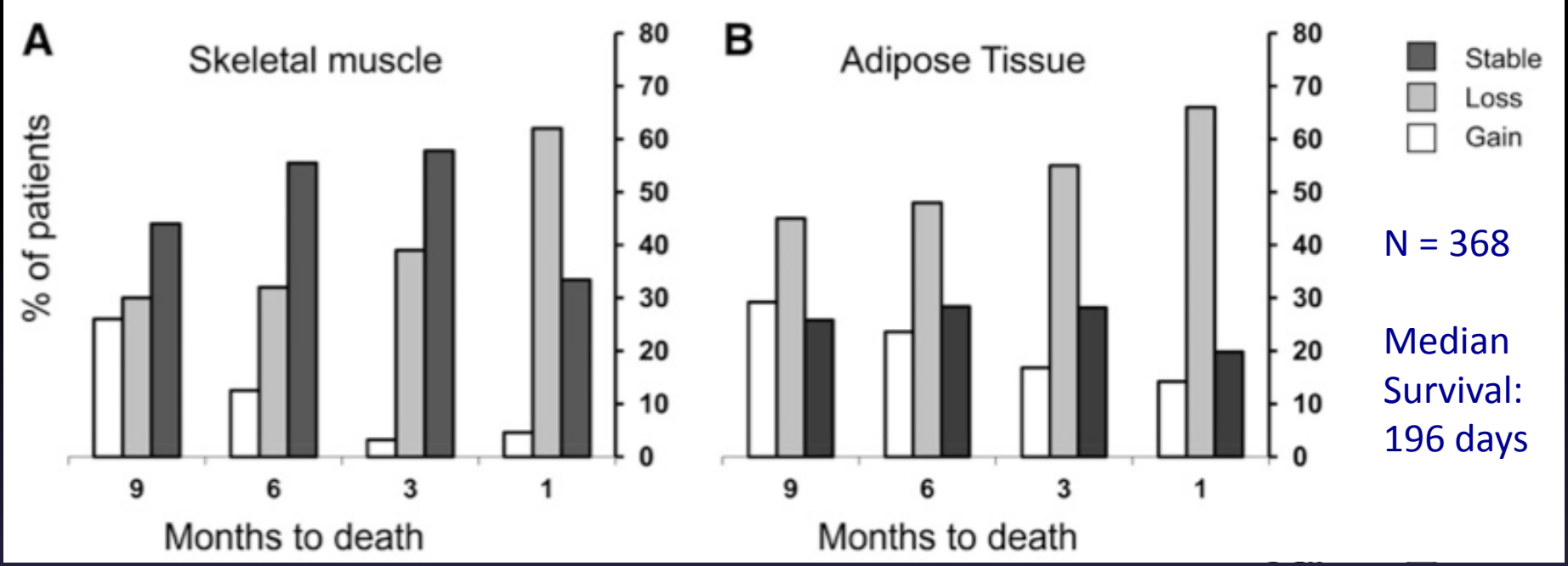
Patient	Protein (g/d)	Fat (g/d)	Fiber (g/d)	CHO (g/d)	Energy intake (kcal/d)*	Energy from CHO (kcal/d)†
1	79.9 ± 28.4	62.5 ± 23.5	9.2 ± 2.3	24.7 ± 6.7	1144 ± 297	98.8
2	81.0 ± 17.5	65.6 ± 18.9	14.4 ± 6.7	36.1 ± 11.4	1034 ± 237	144.4
3	65.9 ± 12.0	63.2 ± 14.7	7.1 ± 2.9	26.1 ± 10.7	1115 ± 183	104.4
4	92. 3 ± 57.9	72.0 ± 45.6	6.4 ± 3.2	27.5 ± 22.8	1137 ± 734	110.0
5	105.5 ± 68.4	83.8 ± 8.1	8.0 ± 3.3	26.6 ± 15.0	1282 ± 410	106.4
6	90.7 ± 35.9	152.0 ± 72.6	9.8 ± 5.7	29.9 ± 10.6	1844 ± 799	119.6
7	71.3 ± 9.5	43.2 ± 9.8	3.8 ± 1.6	11.4 ± 5.7	724 ± 128	45.6
8	162.6 ± 16.3	170.9 ± 44.5	7.3 ± 2.1	48.6 ± 32.0	2397 ± 520	194.4
9	77.3 ± 3.8	43.3 ± 10.2	7.6 ± 2.5	21.0 ± 4.1	784 ± 84	84.0
10	68.8 ± 37.0	57.1 ± 24.9	4.9 ± 5.3	17.7 ± 9.6	898 ± 349	70.8
Mean ± SEM	89.5 ± 8.9	81.4 ± 13.8	7.9 ± 0.9	27.0 ± 3.2	1236 ± 161	107.8 ± 12.7

CHO, carbohydrate
* Macronutrient recall and total energy intake were calculated using Foodworks 11; all values are presented as mean ± SEM during the trial.
† Estimated energy from carbohydrates = 4.0 kcal/g.

- 10 incurable, advanced cancer patients with progressive disease after at least two conventional anticancer treatments
- Physiologic effects:
  - Glucose reduced by 3.2 mg/dL when providing no more than 5% of total energy as carbohydrate for 28 days
    - Extent of ketosis correlated with stable disease or partial remission
  - Weight reduced 3 kg (4%) with 35% energy deficit

Fine EJ, et al. **Nutrition 2012;28:1028-35**

Anabolic Potential in Advanced Cancer



- International consensus group suggested that within 3 months of death, severe muscle wasting, ongoing catabolism, low performance status, & metastatic disease refractory to antineoplastic therapy characterize a cachexia stage that is refractory to treatment[1]

1. ***Fearon K, et al.*** **Lancet Oncol 2011;12:489-95**
2. ***Prado CM, et al.*** **Am J Clin Nutr 2013;98:1012-9**

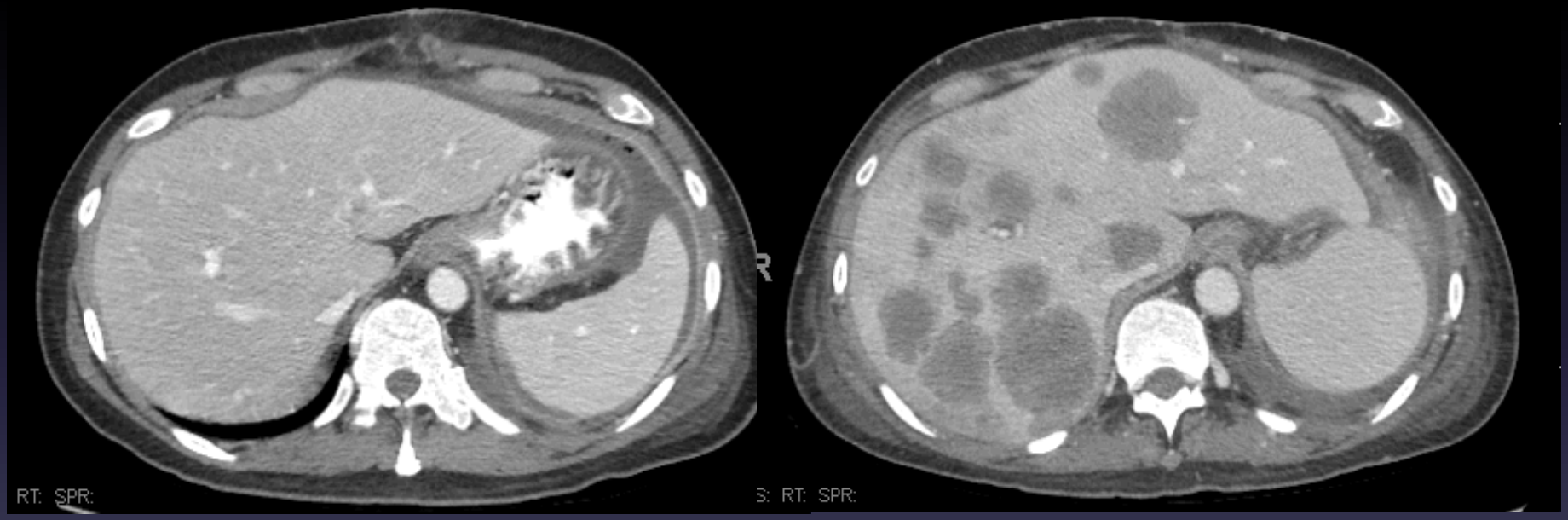
Tumor Growth in Nutrition Support

Parenteral Nutrition in Oncology

Outcome	Absolute Risk Diff	95% CI	# of Studies (Pts)	NNH
Mortality	0%	-5 to 5%	19 (1050)	
Total Complication Rate	40%	14 to 66%	8 (333)	3
Infectious Complication Rate	16%	8 to 23%	18 (823)	6
Tumor Response	-7%	-12 to –1%	15 (910)	14
Bone Marrow Toxicity	22%	-10 to 54%	3 (134)	
Gastrointestinal Toxicity	1%	-9 to 11%	6 (310)	

Koretz RL, et al. **Gastroenterology 2001;121:966-1001**

Tumor Growth in Nutrition Support



C-reactive Protein 75.4 mg/L (2/25/11)
Prealbumin 8.5 mg/dL
Albumin 2.4 g/dL
Weight 59.8 kg

C-reactive Protein 182 mg/L (7/16/11)
Prealbumin < 2 mg/dL
Albumin 2.3 g/dL
Weight 53 kg

Tumor Growth in Nutrition Support

- A review of the literature using PubMed & EMBASE identified 12 suitable papers representing a total of 140 patients receiving nutritional support versus 84 controls
- Studies were classified as randomized clinical trials (n = 5), comparative non- randomized clinical trials (n = 3) & trials with patients who were controls for themselves (n = 4)
- Different indicators of increased tumor cells turnover used in the studies included the DNA index, ornithine decarboxylase activity, flow cytometric DNA distribution, & labeling index with tritiated thymidine or bromodeoxyuridine
- Increased tumor cells turnover was not observed in control patients receiving their usual diet, but it was reported in 7 out of 12 studies in patients receiving nutritional support

Bozzetti F, et al. **Clin Nutr. 2009;28(3):226-30**

Randomized Trials of Tumor Growth

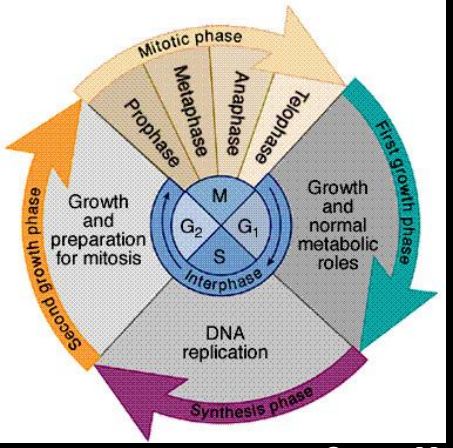
Table 1
Randomized clinical trials in malnourished patients.

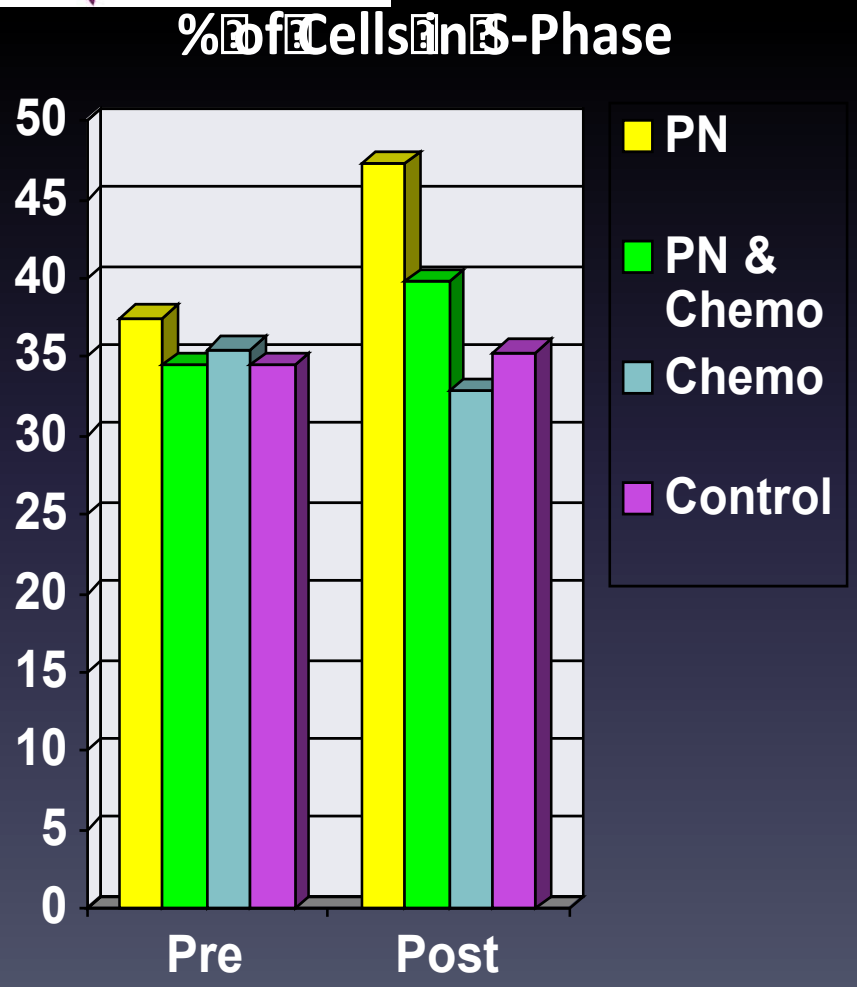
Author	Duration (days)	Controls		Fed		Tumour growth
		No. of pts	Daily nutritional hospital regimen	No. of pts	Daily nutritional support regimen	
Edström[a]	6–8	13	<1000 kcal	13	Harris–Benedict × 1.2–1.5 as EN	No change in controls; significant increase in EN *versus* control pts
Dionigi[b]	8–18	7	19 kcal, 1.1 g AA/kg by mouth or iv	9	42 kcal/kg, 2.3 g AA/kg as TPN or EN	No difference in controls, no difference in fed *versus* control pts
Bozzetti[b]	10	9	Regular diet	10	Harris–Benedict × 1.5 as TPN	No change or ↓ in controls; no change or ↑ in TPN pts
Jin[b]	7	23	Not reported	23	35 kcal and 1.4 g AA/kg as TPN	No change in controls, ↑ significant in TPN pts, ↑ significant in TPN *versus* controls
Pacelli[b]	10–12	10	Standard hospital oral diet	10	30 kcal and 1.2 g AA/kg as TPN	No change in control or TPN pts

Patients and controls were evaluated before and after nutritional support or their usual diet, respectively, and change in the interval was compared between the 2 groups.
EN = enteral nutrition; TPN = total parenteral nutrition; iv = intravenous; pts = patients; AA = amino acid; ↑ means increase, ↓ means decrease.
[a] Patients with head and neck cancer.
[b] Patients with gastrointestinal cancer.

Bozzetti F, et al. **Clin Nutr. 2009;28(3):226-30**

Tumor Growth & PN

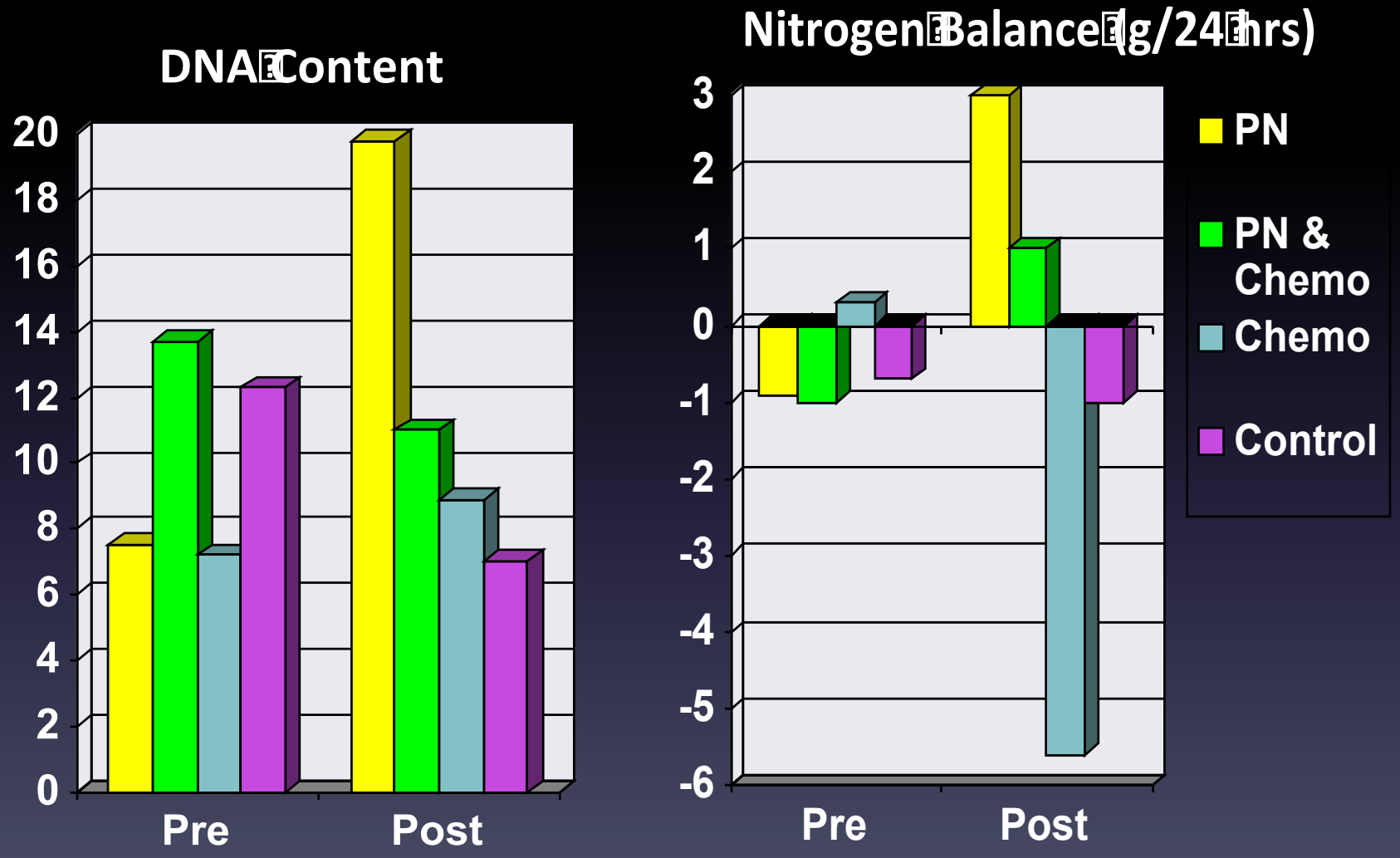




- N = 92: 58 M/34 F, Age 57 yrs
  - 88% gastric, 12% rectal/colon
  - Albumin < 3 or > 10% wt loss
- Randomized to (*N = 23 each*):
  - PN (35 kcal/kg & 1.5 g/kg/d)
    - For 7 days preoperatively
  - PN & Chemo
  - Chemo (5-FU × 7 d, MTX × 1)
  - Control
- Pre- & post-intervention biopsy

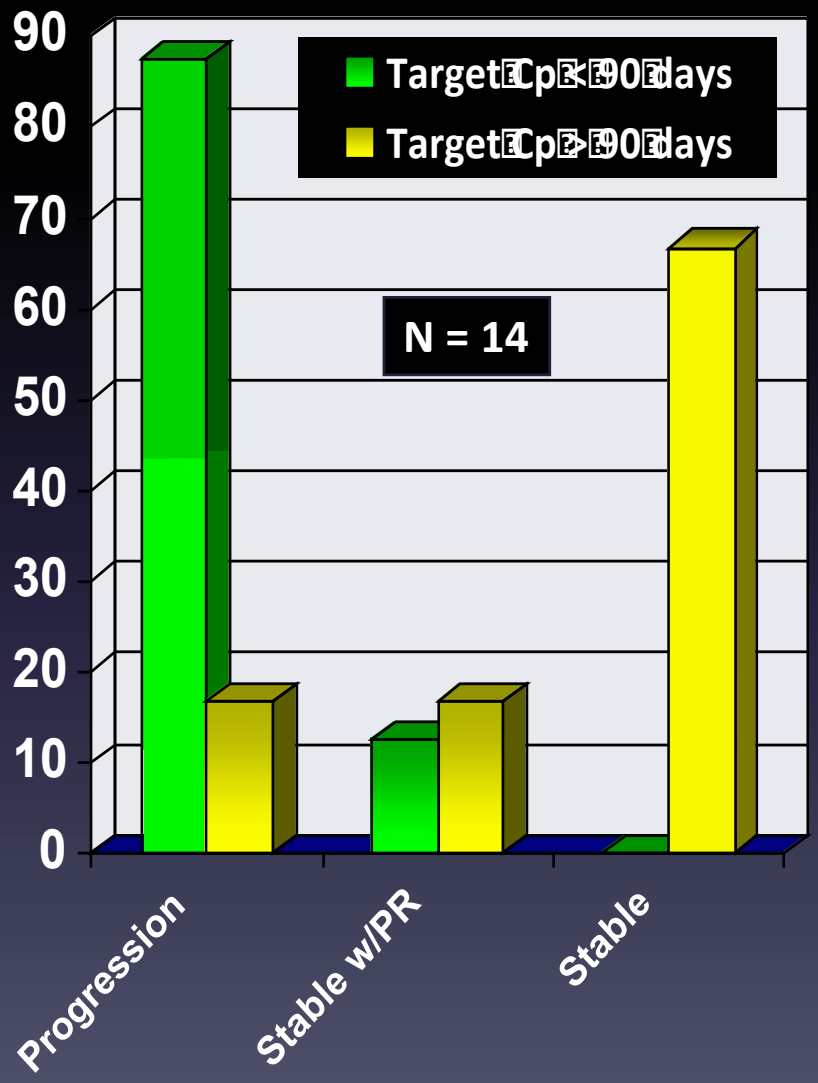
Jin D, et al. **JPEN 1999; 23: 237-41**

Tumor Growth & PN



Jin D, et al. JPEN 1999; 23: 237-41

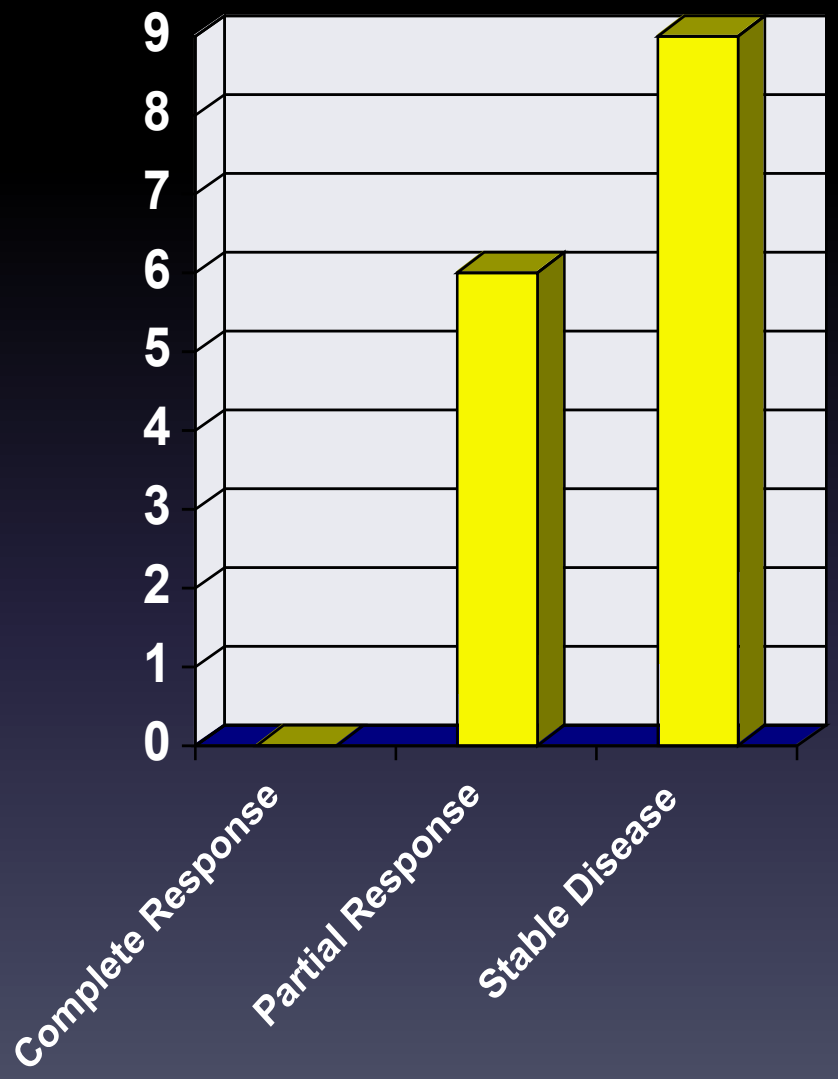
Copper Deficiency in Cancer



- N = 18: 10 M/8 F, Age 59 yrs
  - Metastatic cancer
  - Disease progression in prior 3 months after standard therapies
- Tetrathiomolybdate Phase I trial
  - Forms complex with Cu & protein and when given with food (*prevents Cu reabsorption*)
  - Administered TID w/meals & in-between meals (*6 doses/day*)
    - Goal: 20% of baseline serum ceruloplasmin (Cp)
  - Anemia, defined as hematocrit < 80% of baseline, occurred in approximately one-third of patients

Brewer GJ, et al. **Clin Cancer Res 2000;6:1-10**

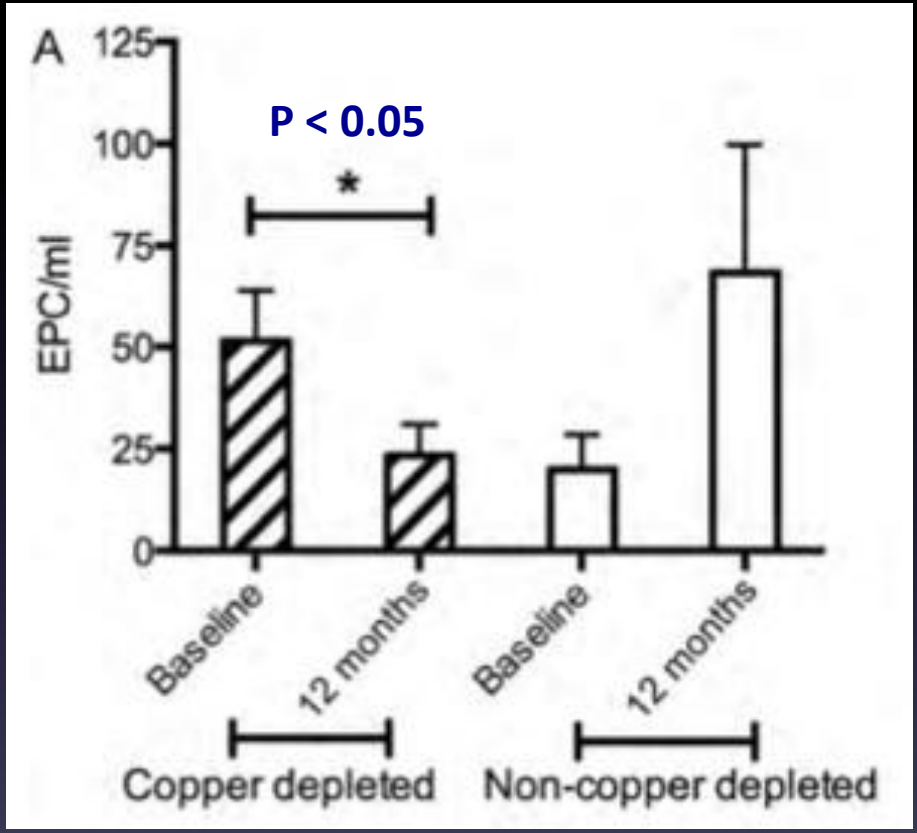
Copper Deficiency in Cancer + Chemotherapy



- N = 24: 18 M/6 F, Age 57 yrs
- Irinotecan 125 mg/m^2, 5-Fluorouracil 500 mg/m^2, leucovorin 20 mg/m^2 on days 1, 8, 15, and 22 of a 6 week cycle for metastatic colorectal cancer for up to 6 months
- Tetrathiomolybdate Phase II trial
  - Initiated on day 1 of cycle 1 at 40 mg three times daily with meals and 60 mg before bed without food & decreased with target Cp level of 5– 15 mg/dL
  - Median Time to Progression from time of enrollment was 5.6 months (95% CI 2.7–7.7 months)

Gartner EM, et al. **Invest New Drugs 2009;27:159-65**

Copper Deficiency in Breast Cancer



- N = 39 females: Age 50 yrs
  - Histologically confirmed stage 3, stage 4 with NED, or stage 2 triple-negative breast cancer
- Tetrathiomolybdate Phase II trial
  - Effects on bone marrow-derived endothelial progenitor cells (EPC) for up to 2 years
  - 180 mg daily in four divided doses until Cp levels decreased to target range of 5–16 mg/dL
  - 27 patients (69%) remain relapse-free on study extended to 6 years

Jain S, et al. **Ann Oncol 2013;24:1491-8**

Medical Marijuana

Therapeutic Uses of Medical Marijuana in Cancer

- Cannabinoids are a class of > 60 compounds derived from the plant *Cannabis sativa*
  - Tetrahydrocannabinol (THC) is most widely studied
  - Produces mood alterations, sedation, increased appetite, hallucinations & impairment of memory, coordination & executive function
  - Analgesia occurs at higher concentrations
    - Role in the palliation of neuropathic pain, muscle spasms & appetite
    - Adjunctive in managing nausea / vomiting associated with chemotherapy
    - Potential direct anti-tumorigenic & anti-angiogenic properties

Cridge BJ, et al. **Cancer Manag Res 2013;5:301-13**

Table 1. States with Enacted Laws to Allow Marijuana Use for Medical Purposes[12]

State	Year Passed	Possession Limit
Alaska	1998	1 oz usable; 6 plants (3 mature, 3 immature)
Arizona	2010	2.5 oz usable; 0–12 plants[a]
California	1996	8 oz usable; 6 mature or 12 immature plants
Colorado	2000	2 oz usable; 6 plants (3 mature, 3 immature)
Connecticut	2012	1-mo supply (exact amount to be determined)
District of Columbia	2010	2 oz dried; limits on other forms to be determined
Delaware	2011	6 oz usable
Hawaii	2000	3 oz usable; 7 plants (3 mature, 4 immature)
Maine	1999	2.5 oz usable; 6 plants
Massachusetts	2012	60 day supply for personal medical use
Michigan	2008	2.5 oz usable; 12 plants
Montana	2004	1 oz usable; 4 plants (mature), 12 seedlings
Nevada	2000	1 oz usable; 7 plants (3 mature, 4 immature)
New Jersey	2010	2 oz usable
New Mexico	2007	6 oz usable; 16 plants (4 mature, 12 immature)
Oregon	1998	24 oz usable; 24 plants (6 mature, 18 immature)
Rhode Island	2006	2.5 oz usable; 12 plants
Vermont	2004	2 oz usable; 9 plants (2 mature, 7 immature)
Washington	1998	24 oz usable; 15 plants

[a]If the patient lives > 25 miles from the nearest dispensary, the patient or caregiver may cultivate up to 12 marijuana plants in an enclosed, locked facility.

Borgelt LM, et al. **Pharmacotherapy 2013;33:195-209**

Medical Marijuana in Cancer

- Nabilone is not recommended as treatment option in NCCN Guidelines for preventing CINV
  - Recommended at 1 to 2 mg orally every 12 hours for breakthrough nausea & vomiting
- Dronabinol is synthetic THC
  - NCCN does not recommend dronabinol for prevention of CINV, but recommends 5 to 10 mg orally every 3 or 6 hours for breakthrough nausea and vomiting
- Adverse effects of ataxia, anxiety, disorientation, hallucinations, depression & psychosis limit their use

Todaro B. **J Natl Compr Canc Netw 2012;10:487-492**

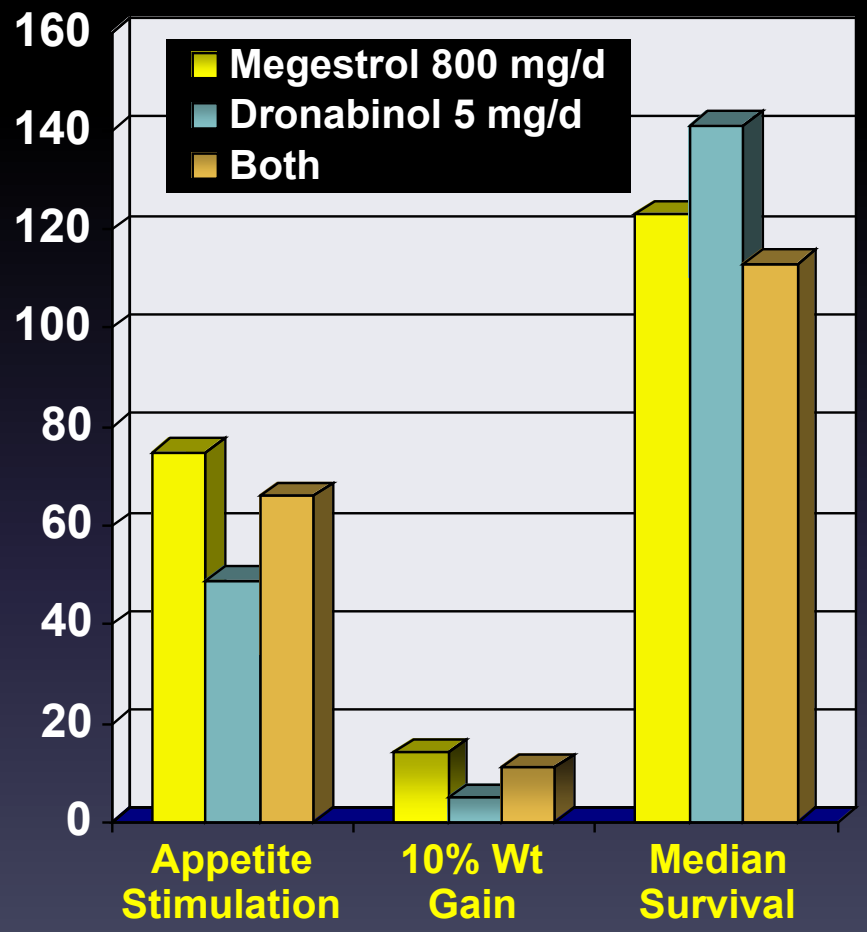
Medical Marijuana in Cancer

- Determining dosages of THC given various routes of delivery
  - Low dose as < 7 mg
  - Medium dose as 7–18 mg
  - High dose as > 18 mg
- However, there is known tolerance to THC through downregulation of CB1 receptors
  - High probability of tolerance with as few as 4 days of daily use and low probability with intermittent use
- Levels of hormones such as luteinizing hormone, follicle-stimulating hormone, prolactin & growth hormone are known to decline with long-term exposure

Borgelt LM, et al. **Pharmacotherapy 2013;33:195-209**

Combination Therapy – Is It Better?

- N = 469: 65% M/35% F, Age 67 yrs
  - 45% Lung, 30% GI cancer
  - 60% with > 10 lb wt loss in 2 mos
- Double-blind, randomized trial
  - Megestrol 800 mg po daily + placebo
    - Median duration 80 days
      - Withdrawal / Death 67%
  - Dronabinol 2.5 mg po BID + placebo
    - Median duration 57 days
      - Withdrawal / Death 73%
  - Megestrol 800 mg po daily + Dronabinol 2.5 mg po BID
    - Median duration 74 days
      - Withdrawal / Death 67%



Jatoi A, et al. J Clin Oncol 2002;20:567-73

Conclusions

- Dietary restriction or short term starvation may offer additional benefit for cancer patients receiving chemotherapy
  - Ketosis will need further study in humans with cancer
  - Copper deficiency may be effective in advanced cancer
- Nutrition support will result in tumor growth & patients should be informed of the risk
- Medical marijuana can be used as an adjunct for pain, nausea / vomiting & appetite
  - Further study needed to elucidate benefits vs. toxicity