Omega 3 Fatty Acids and Starvation in Cancer Patients

Aminah Jatoi, M.D.
Department of Oncology
Mayo Clinic
Rochester, Minnesota

September 10, 2009

- Why focus on cancer-associated weight loss? Why focus on fish oil?
- What can we learn from phase III trials in incurable cancer patients? What about other patients (gaps)?
- Do preclinical data warrant further exploration of starvation in cancer patients (gaps)?

Effect of Weight Loss on Survival

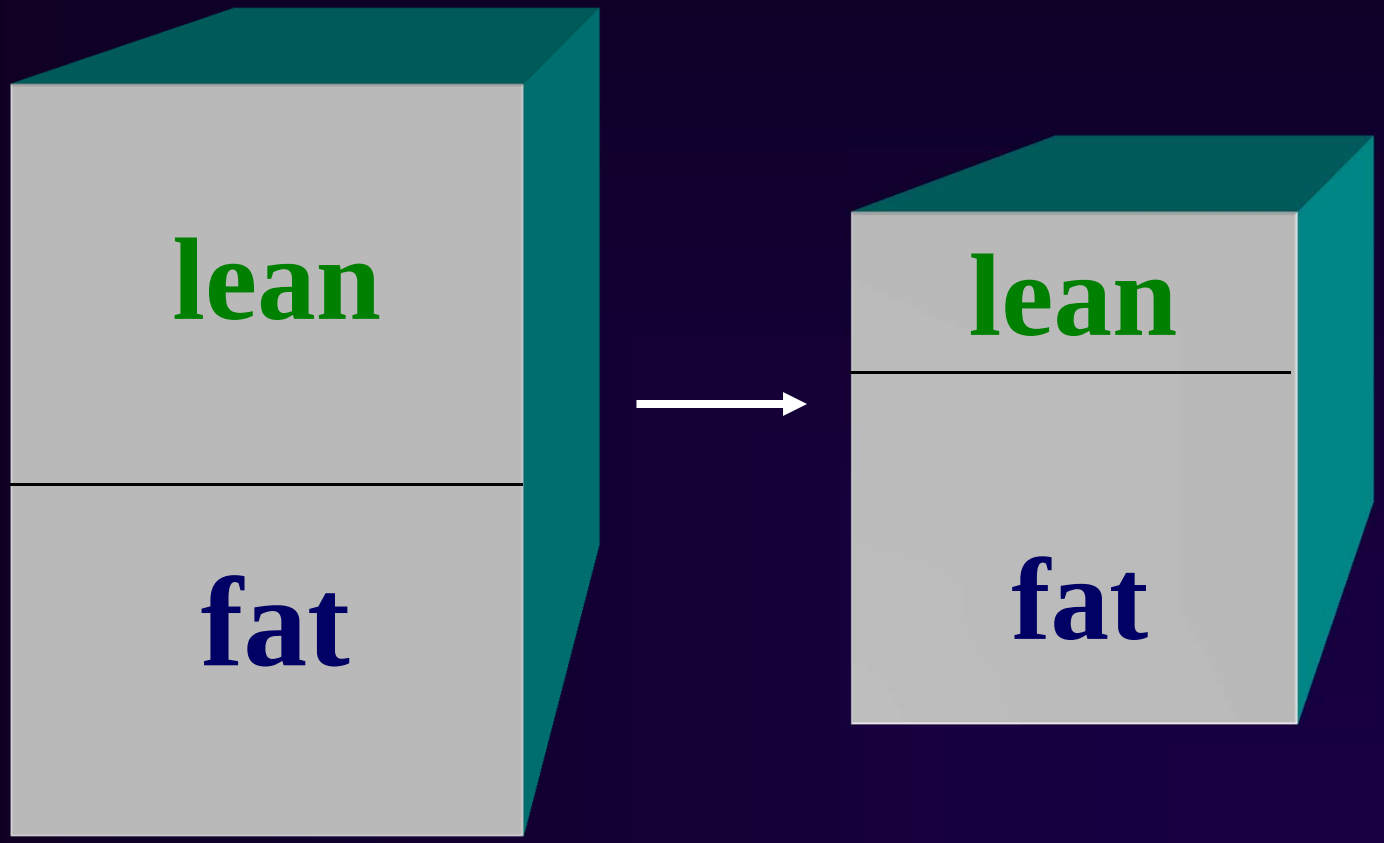
	Median Survival (weeks)		
Tumor Type	**No Weight Loss**	**Weight Loss**	**P-Value**
Breast	**70**	**45**	**< 0.01**
Colon	**43**	**21**	**<0.01**
Prostate	**46**	**24**	**<0.05**
Lung, small cell	**34**	**27**	**<0.05**
Lung, non-small cell	**20**	**14**	**<0.01**
Pancreas	**14**	**12**	**N.S.**

Adapted from *Am J Med* 69:491-7, 1980.

“Malnutrition could effect survival… by muscle wasting and susceptibility to infections… much of the weight loss would be drawn from lean body tissue…”

Am J Med **69:491-7, 1980.**

The importance of lean tissue….



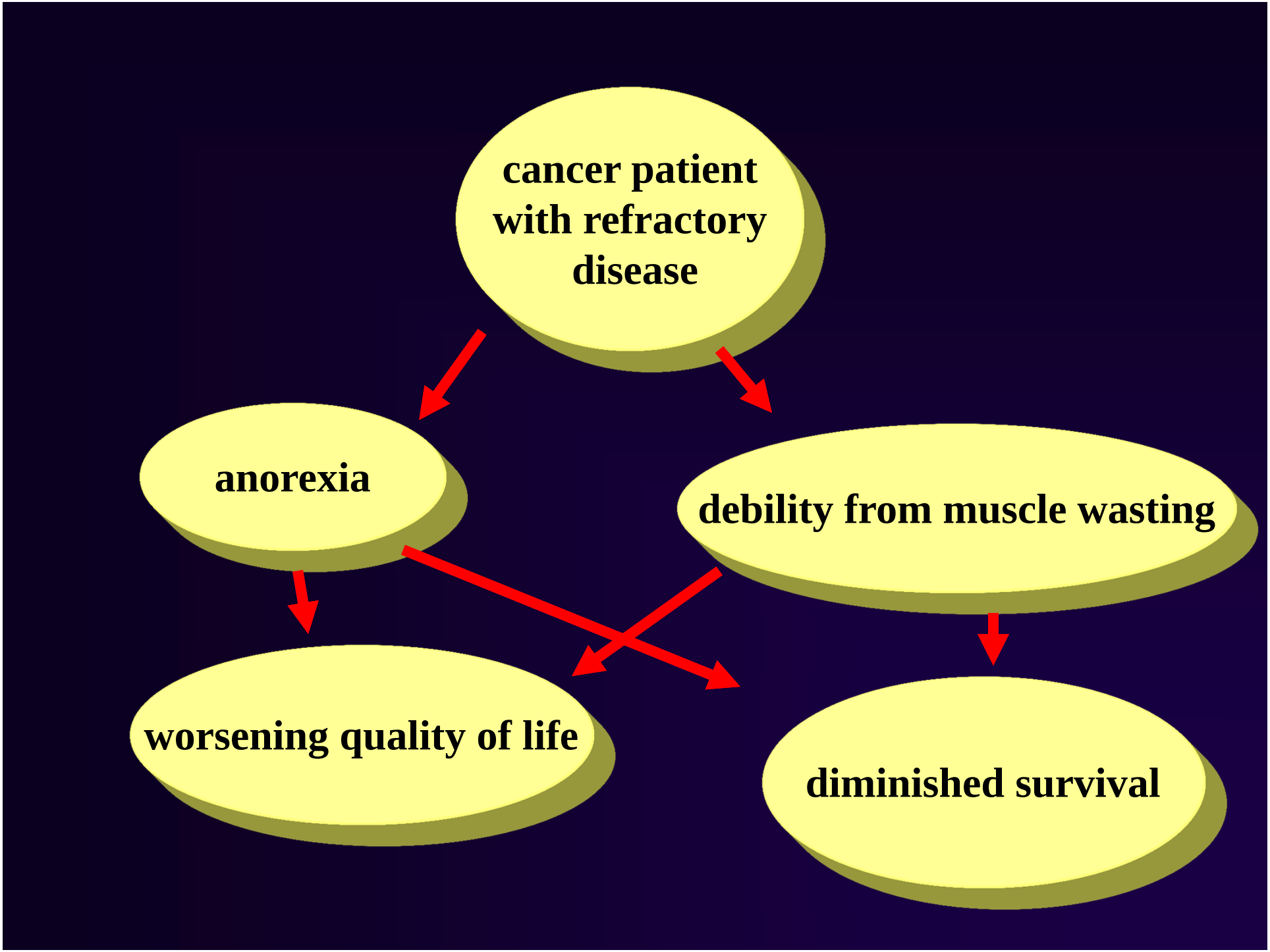
cancer-free

cancer-laden

Patient Survival by Physical Symptoms

Variable	Score	N	median survival (days)	P
Loss of appetite	25	36	93	0.0015
	50	22	116	
	75	27	37	
	100	14	21	
Nausea	25	70	75	0.005
	50	21	56	
	75	6	13	
	100	3	48	
Vomiting	25	76	75	0.0167
	50	20	45	
	75	2	12	
	100	2	42	

Adapted from *J Pain Symptom Manage* 11:32-41, 1996.


cancer patient with refractory disease
anorexia
debility from muscle wasting
worsening quality of life
diminished survival

Rationale for studying EPA and other fish oils:

- anti-inflammatory effects: cytokine and proteasome suppression
- early clinical data appeared promising

	3 weeks	7 weeks
# of patients	**18**	**13**
weight change	***+1***	***+2***
change in lean mass	***+1***	***+1.9***
change in performance score (Karnofsky)	***+10***	***+10***
change in appetite	***+1***	***+1***

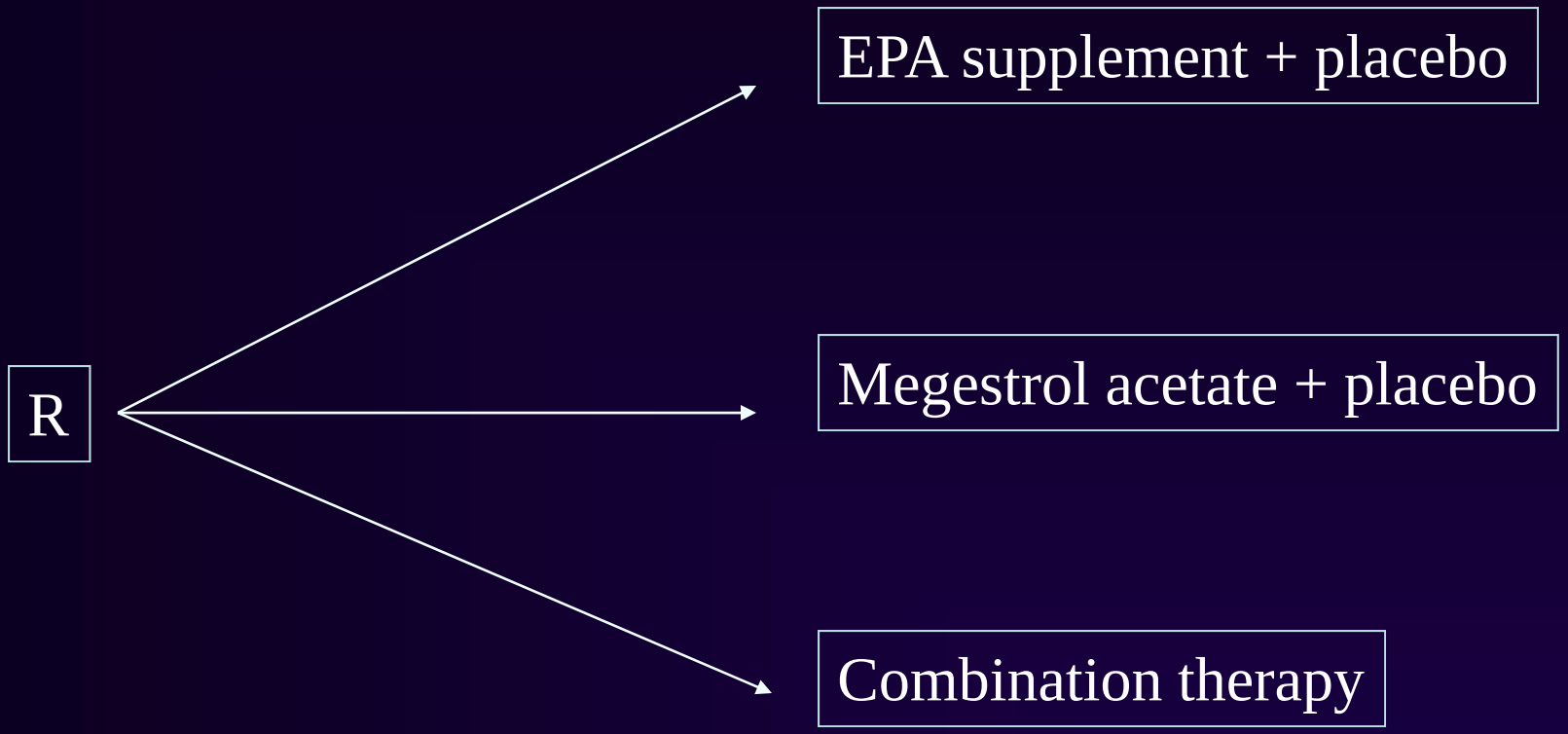
Barber, et al. *Br J Cancer* 81:80-86, 1999.

A survival advantage was observed in a 60-page randomized trial.

Gogos, et al

- Why cancer-associated weight loss? Why fish oil?
- What can we learn from phase III trials in incurable cancer patients? What about other patients (gaps)?
- Do preclinical data warrant further exploration of starvation in cancer patients (gaps)?

4 large comparative trials….



DOUBLE-DUMMY DESIGN

BASELINE CHARACTERISTICS:

	EPA-supplemented (N=141)	Megestrol acetate (N=140)	combination (N=140)	P-value
AGE	66	65	66	0.44
SEX	M>F	M>F	M>F	0.40
CANCER				
lung	39%	39%	40%	0.94
gastrointestinal	32%	33%	36%	
other	29%	28%	24%	
WEIGHT LOSS (≥ 10 pounds)	61%	63%	61%	0.93

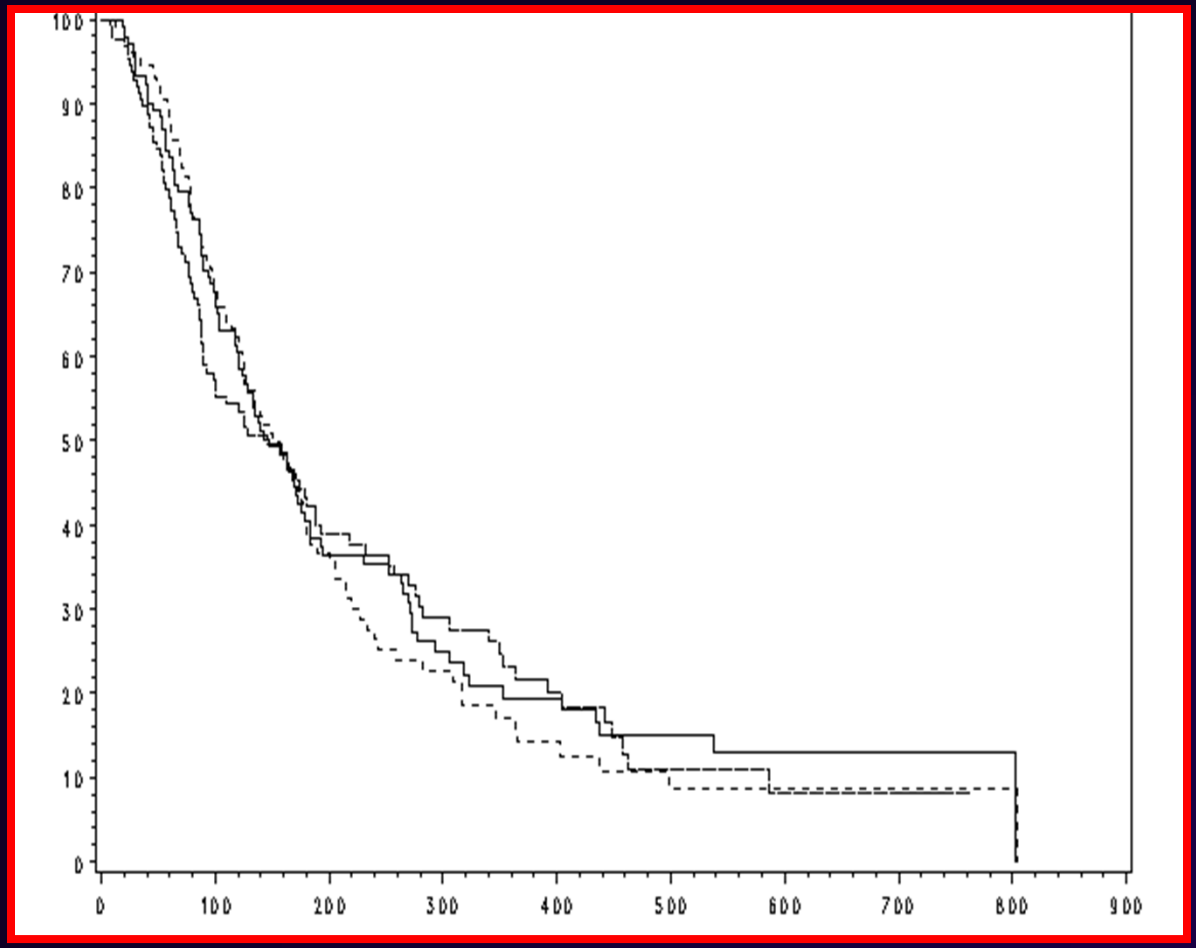
Primary endpoint: ≥ 10% non-fluid weight gain :

EPA-treated (N=141):	6%
Megestrol acetate-treated (N=140):	18%
Combination-treated (N=140):	11%

P-value (over all groups): 0.01

No improvement in quality of life with EPA.

WAS THERE A SURVIVAL ADVANTAGE?



TOXICITY	%EPA-treated	% megestrol acetate-treated	% combination therapy	P-value (over all groups)
impotence	3	9	19	0.0006
blood clot	6	8	2	0.63

>1000
cancer patients later:

“The results indicate no statistically significant benefit…. Future studies should concentrate on other agents or combination regimens.”

Fearon K, et al *JCO* 24:3401-7, 2006

CONCLUSION:

There were insufficient data to establish whether oral EPA was better than placebo.

Cochrane Review, 2007

GAPS
(my opinion)

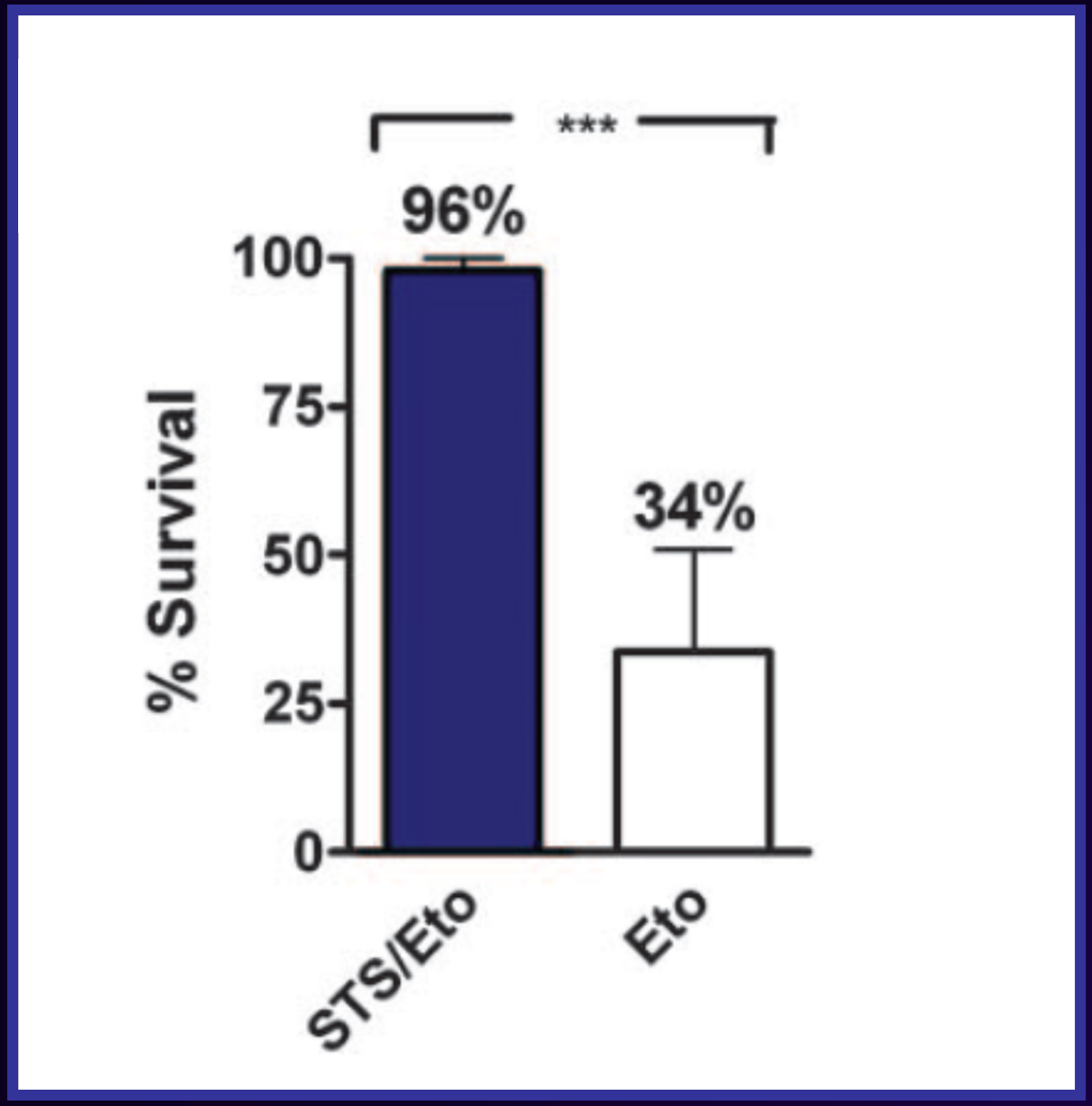
- Why cancer-associated weight loss? Why fish oil?
- What can we learn from phase III trials in incurable cancer patients? What about other patients (gaps)?
- Do preclinical data warrant further exploration of starvation in cancer patients (gaps)?

Hypothesis:

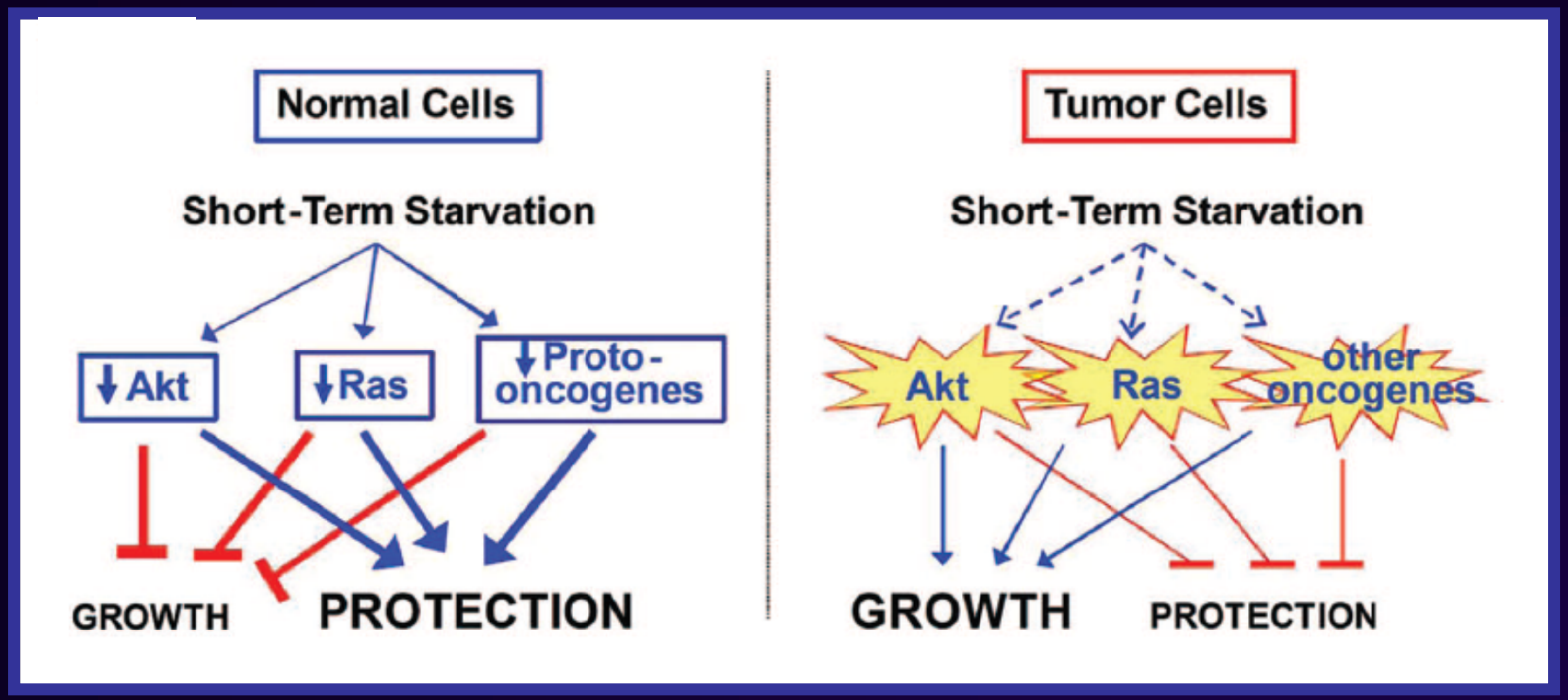
Fasting slows metabolism in normal cells and therefore leads to less chemotherapy-induced toxicity.

Because cancer cells, are unregulated, they continue to be vulnerable to chemotherapy even during fasting.

Starvation Prior to Chemotherapy Resulted in Improved Survival:



Raffaghello L, et al. PNAS, 2008


Normal Cells
Short-Term Starvation
↓Akt
↓Ras
↓Proto-oncogenes
GROWTH
PROTECTION
Tumor Cells
Short-Term Starvation
Akt
Ras
other oncogenes
GROWTH
PROTECTION

Why might fasting, alternate day feeding, or caloric restriction benefit cancer patients?

- shifting metabolism
- anti-oxidant effects

Should we recommend that patients fast prior to chemotherapy?

No.

- “Would I be enthusiastic about enrolling my patients on a trial where they’re asked not to eat for 2 1/2 days? No.”

  – Leonard Saltz, M.D.

- “… it really goes against a lot of the thoughts that people have, that you need to eat to feel better.”

  – Alan Sandler, M.D.

Couzin J. Science, 2008

Ongoing Clinical Trials

- NCT00757094: King Fahad Medical City; tests the safety of fasting before chemotherapy during Ramadan

- University of Southern California: trial in development; funded by the V Foundation

Gaps
(my opinions)