

Micronutrient Status and the Nervous System in Cancer : A Balance between Feeding the Host and Starving the Tumor



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Feeding the host



Starving the tumor



Feeding the host



Starving the tumor



Nutrition, the Nervous System and Cancer

- Neurological complications may occur in cancer patients through several mechanisms
 - Chemotherapy-related neurotoxicity
 - Tumor – associated neurotoxicity
 - Other underlying neurological, or systemic disease
- **Question:** What is the role of nutrition?

Neoplasia & Neurotoxicity; Nutrition and Neuroprotection

- Issues, Problems and Questions
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 - If nutrient-related, is PNP nutrient-responsive?
 - Is PNP ameliorated or aggravated by micronutrient supplementation?.

Neurological complications of Systemic Cancer

- Neurological complications of varying severity may occur in cancer patients, arising through several mechanisms.
 - Early detection and intervention important.
 - Affected anatomical site varies (brain, cord, peripheral nerve).
 - Chemotherapy-related neurotoxicity
 - Paraneoplastic antibodies.
 - Nutritional causes are uncommon.
- **Approach:** Signs, symptoms, laboratory, imaging, other tests to identify underlying cause.

Host vs Tumor Competition – Several Battlegrounds

Tumor-host competition occurs at several levels

- Physical (anatomical) space.
 - Immune surveillance and evasion.
 - Blood supply.
 - Nutrient supply
-
- **Question:** What is the role of nutrition?

Micronutrient Status and the Nervous System in Cancer

- Causes of micronutrient deficiency states in cancer.
 - Tumor-host competition for nutrients.
 - Chemotherapeutic agents designed to disrupt nutrient-dependent pathways (dihydrofolate reductase inhibitors, e.g. MTX).
 - Chemo- or radio- therapy that interdicts vitamin absorption or metabolism.
 - Generalized cachexia with resulting global marasmic undernutrition.
 - Pre-existing underlying deficiency.
- **Problem:** How to protect or rescue the host nutritionally without feeding the tumor?

Host vs Tumor Competition - Nutrition and Brain Function

Tumor-host competition for nutrients

- An adequate supply of critical micronutrients is essential for maintenance of normal and malignant cell growth.
- Tumor cells are highly effective in competing with normal cells for available micronutrients.
- This may lead to or aggravate host nutrient deficiencies.
- **Question:** How can normal cells be protected without “stoking” malignant cell growth?

Neurotoxic Complications of Chemotherapy in Cancer Patients

- Neurotoxic side effects of chemotherapy are frequent and are often the reason to limit chemotherapy dose.
- Bone marrow toxicity can be overcome with growth factors or BMT.
- This results in the use of higher doses of chemotherapy which further increases the risk of neurotoxicity.
- Chemotherapy may cause peripheral or central neurotoxicity.

Chemotherapy-Related Neurological Complications in Cancer

- May affect either or both the central or peripheral nervous system.
- Central effects may range from mild cognitive impairment to encephalopathy, dementia and coma.
- Peripheral effects usually consist of peripheral neuropathy.
- Both central and peripheral neurotoxicity may further aggravate underlying existing neurological disease

Neurotoxic Complications of Some Cancer Chemotherapeutic Agents can Mimic Micronutrient Deficiencies

■ Examples

- Cisplatin can cause paresthesias, loss of proprioception, ataxia and Lhermitte's sign that closely resemble cobalamin and other micronutrient deficient neuropathies.
- Docetaxel can cause neuropathy, predominantly sensory, with loss of deep tendon reflexes and vibration sensation resembling long-tract spinal cord lesions seen in cobalamin and other micronutrient deficiencies and sometimes responsive to pyridoxine

The Central Nervous System as Sanctuary

- Certain cancers show a predeliction for homing and “hiding” in the CNS (example childhood ALL).
- Neural stem cells reside in the CNS.
- The CNS has certain features that distinguish it from other tissues
 - It is extremely sensitive to damage by many chemotherapeutic agents as well as to nutrient deprivation.
 - Cytotoxic effects in the CNS are generally irreversible and poorly responsive to treatment.
 - Cellular rescue therapy is currently not available.

Chemotherapy-Related Neurological Complications in Cancer

- Chemotherapy drugs commonly causing neurotoxicity.
 - Vinca alkaloids, cisplatin and taxanes (used for ovarian, breast, hematological cancers) frequently cause peripheral neurotoxicity
 - MTX, cytarabine and ifosfamide primarily cause central neurotoxic side effects (high doses, frequent administration and preceding radiotherapy aggravate neurotoxicity).
- Management of neurotoxicity consist of lowering dose and frequency of drugs and the use of “neuroprotective agents”

Neurotoxic Drugs and Neuroprotective Agents

Agent	Side Effects	Treatment
Cisplatin	Sensory deficits resembling B12 deficiency	Glutathione Amifostine – thiol Org 2766 – synthetic ACTH
Vinca alkaloids	Varied – mainly peripheral neuropathy	Glutamic acid Org 2766
Taxanes - Docitaxel	Sensory, resembling B12 deficiency, proximal motor weakness	pyridoxine
Methotrexate	<ul style="list-style-type: none"> - Varied, immediate, intermediate and late - Confusion, ataxia, leukoencephalopathy - <10% with i.v. - 40%+ with intrathecal 	Folinic acid - efficacy questioned - may allow repeat dosing after leukoencephalopathy ? rescues neural stem cells



Examples of Reported Micronutrient Deficiencies Affecting the Nervous System in Cancer

- Thiamine deficiency resulting in Wernicke's encephalopathy in patients with severe cachexia.
- Cobalamin deficiency resulting from excessive consumption by the tumor or malabsorption following surgical resection or pelvic irradiation.
- **Question:** Should nutrient supplements be given to :
 - All cancer patients?
 - Cancer patients receiving regimens known for neurotoxicity?
 - Patients who manifest neurotoxicity

Dana-Farber Regimen for Peripheral Neuropathy in Multiple Myeloma



Hi-Dose Multi-B Complex Vitamins with B1, B 6, **B12**, folic acid and other B-vitamins

Folic acid 1-2 mg.

B6 approximately 100mg qd, not to exceed 200 mg

Vitamin E—400 IU daily

Fish Oils-Omega3 fatty acids EPA and DHA

Evening Primrose Oil Capsules

Flax Seed Oil

Amino Acids

Acetyl L- Carnitine—500 mg with food-1-2 hrs before or after twice daily

Alpha-Lipoic Acid 200 mg a day

Acetyl L Carnitine 500 mg



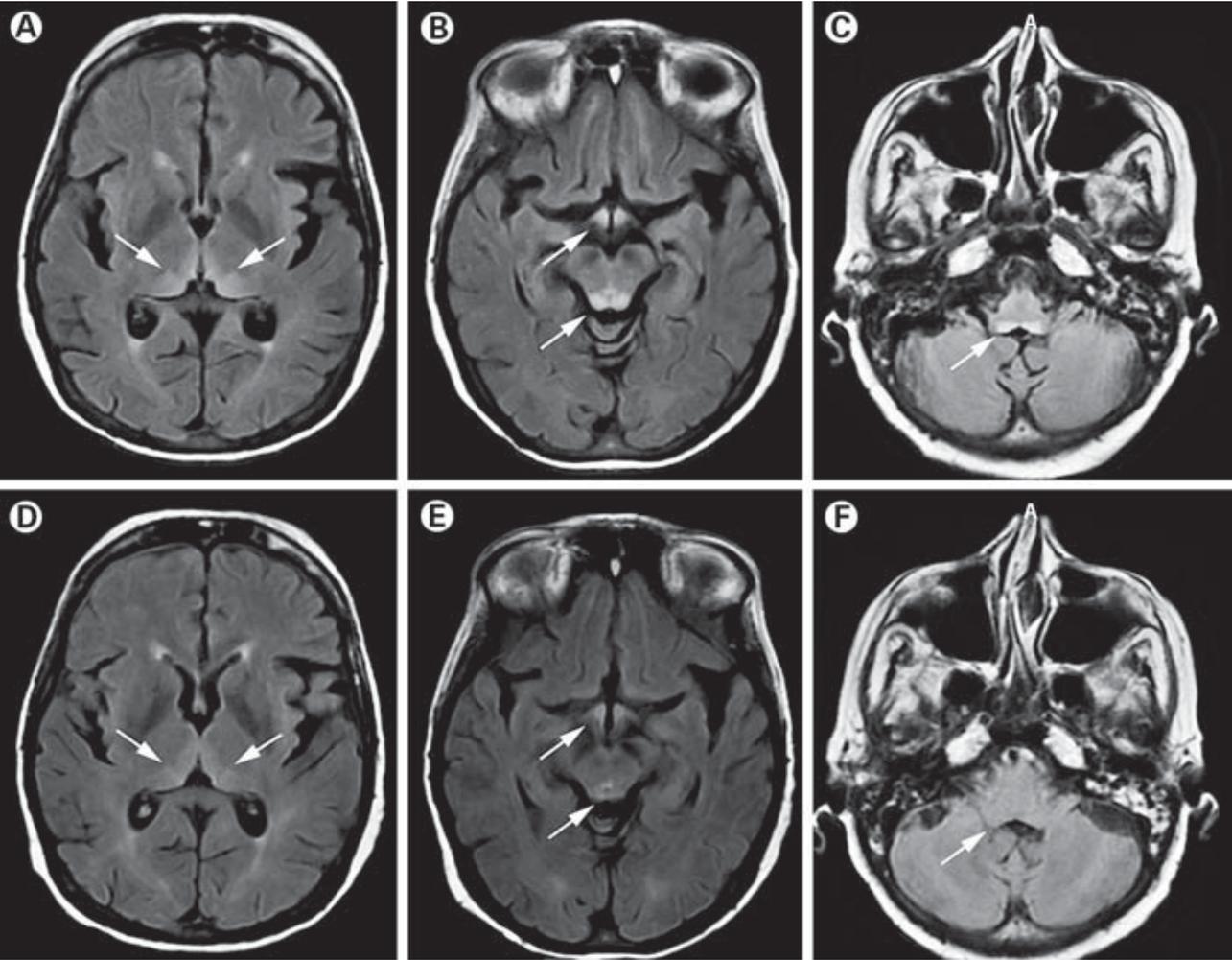
Wernicke's Encephalopathy Caused by Thiamine Deficiency in Cancer Patients

- WE is a neurological emergency
- Rapid onset of symptoms of confusion, ophthalmoplegia and ataxia
- Predisposing factors in cancer patients include:
 - Chronic malnutrition
 - Chemotherapy-induced N & V
 - Thiamine consumption by rapidly growing tumor cells

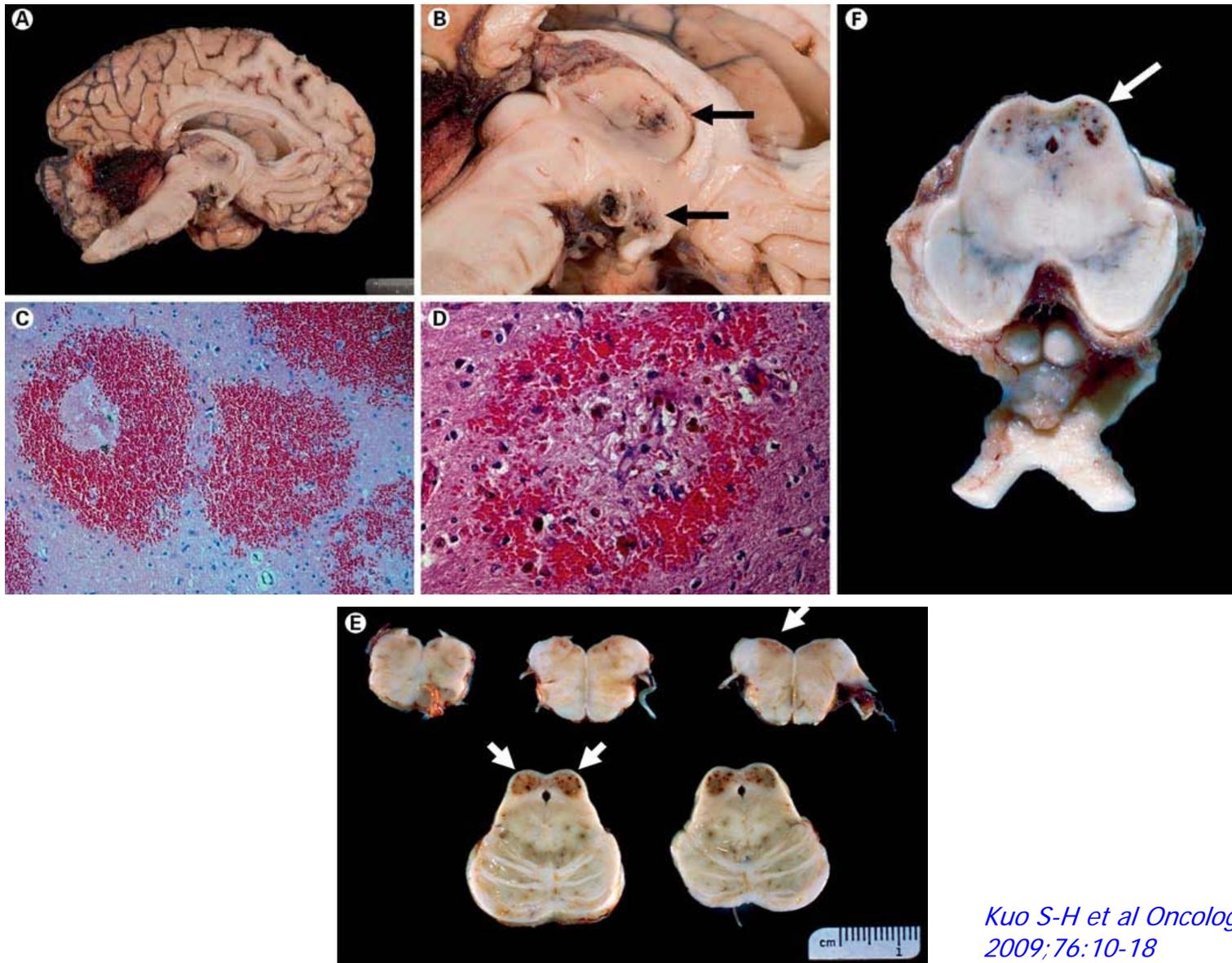


All cancer patients with confusion should be treated empirically with thiamine by injection

**Axial Brain MRI and FLAIR Before (A,B,C) and After (D,E,F)
Treatment with Thiamine for 7 Days**



Autopsy Findings in the Brain of a Cancer Patient with Wernicke's Encephalopathy



Modified* Dana-Farber Regimen for Peripheral Neuropathy in Multiple Myeloma

A daily multivitamin.

A good multi-B (e.g. B-100), with added B6 if necessary to get 50 to 100 mg/day but not more than 100 mg.

Vitamin B-12 sublingual 1000 mcg daily.

Alpha-lipoic acid 300 mg twice daily.

Acetyl-L-carnitine 500 mg twice daily.

Vitamin E 400 to 800 IU daily, but not more than 800.

L-glutamine 15 to 30 grams per day. Wow.

Curcumin 500 mg daily.

Flax seed oil 1000 mg per day. Maybe fish oil too, but I need a reliable source.

Bromelain, amount undetermined just now.

Caveat: Nutrient/vitamin cocktails may ameliorate peripheral neuropathy, but may also “feed” tumor cells and promote tumor growth.

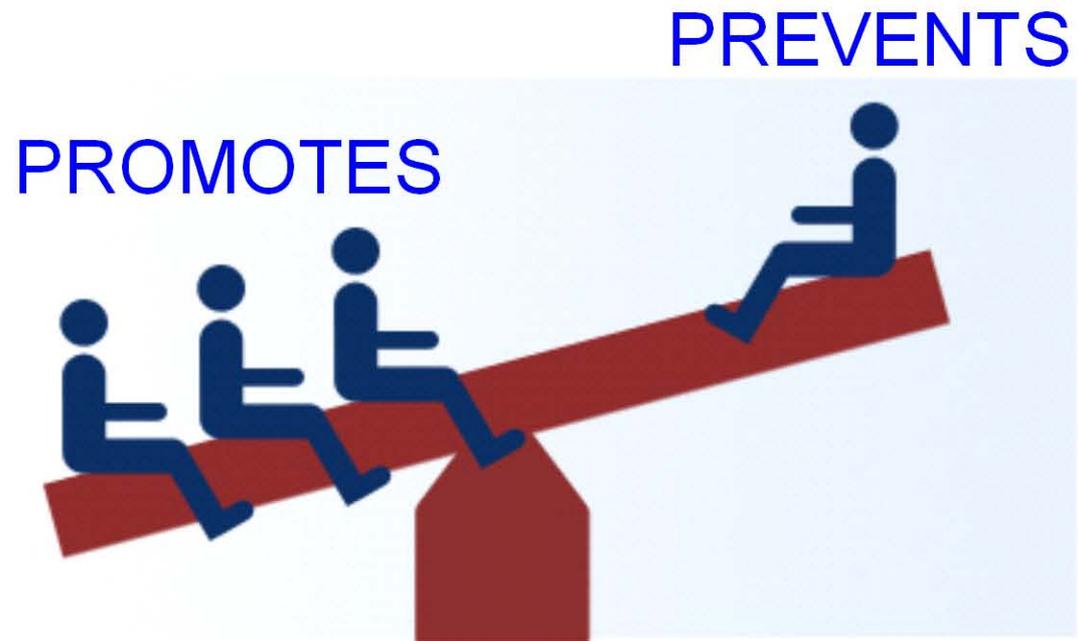
* <http://myelomahope.blogspot.com/2009/05/peripheral-neuropathy.html>

Baz R, Alemany CA, Green R, Hussein MA: *Prevalence of Vitamin B12 deficiency in patients with plasma cell dyscrasias: a retrospective review. Cancer. 101: 790-5; 2004.*

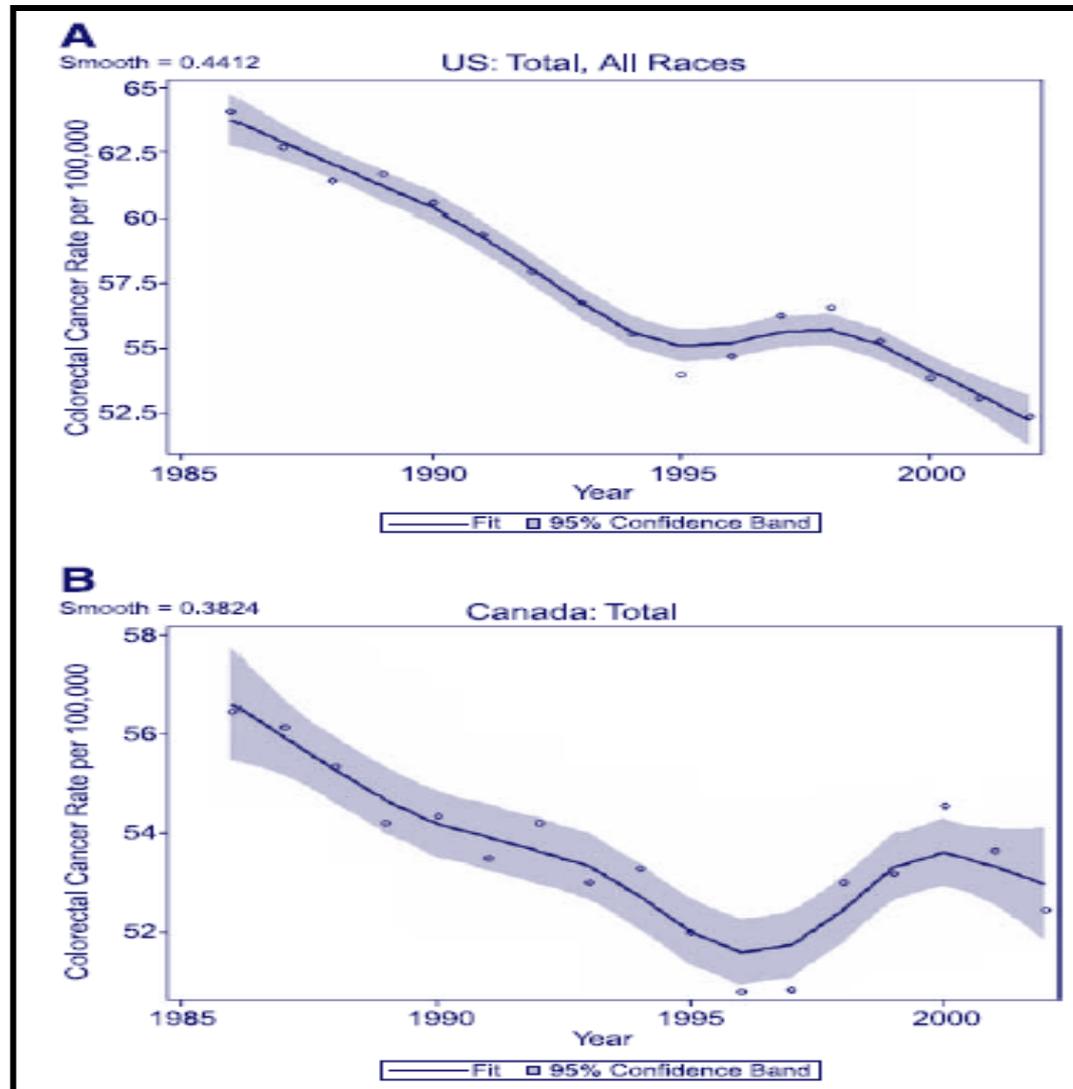
The findings of the current study indicate that vitamin B12 deficiency is prevalent among patients with PCD. **Among 522 patients, 71 (13.6%) had laboratory-defined vitamin B12 deficiency.**

Neither MCV nor the presence of anemia is predictive of this deficiency. Serum vitamin B12 measurement should be part of the initial evaluation of patients with PCD and should not be restricted to patients with anemia, macrocytosis, and unexplained neuropathy. **Identifying vitamin B12 deficiency is especially important in patients receiving active therapy for MM that has potential neurotoxic side effects.** When patients with PCD develop neuropathy, it is often attributed to their PCD or to the side effects of chemotherapeutic agents used for its therapy. Vitamin B12 deficiency is not primarily considered a causative factor. Conversely, **peripheral neuropathy often limits the use of active antimyeloma agents in patients with recurrent or refractory MM.** Eliminating confounding neuropathy caused by vitamin B12 deficiency would increase the clinical use and decrease the discontinuation of active antimyeloma agents such as thalidomide, vincristine, arsenic trioxide, and bortezomib.

FOLATE AND CANCER



Incidence of Colorectal Cancer In US and Canada



Feeding the host



Starving the tumor



To protect the nervous system in cancer, the goal of feeding the host and starving the tumor is a balancing act.....



Thank you!