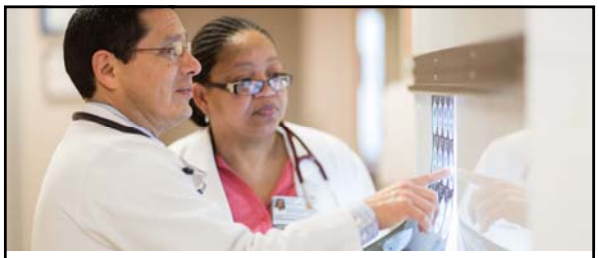

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Management of Diabetes in Patients with Cancer
Part 1

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Disclosure

Nothing to Disclose

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Objectives

- Explain the relationship between diabetes and cancer.
- Identify ways to evaluate glucose control in persons with glycemic dysregulation and cancer.
- Describe the importance of evaluating the persons individual oncology treatment plan.

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What we will cover:

- Relationship between diabetes and cancer
- Evaluation of glucose control
- Imaging
- Treatment options currently used
- Chemotherapy
- Immunotherapy
- Stem Cell transplant
- Surgery
- CART

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A Little Bit About Us

The M.D. Anderson Diabetes program consist of 3 Diabetes Physicians and 5 Nurse Practitioners.

We rotate between Inpatient and Outpatient duties.

We see patients who are admitted with elevated glucose readings and in the outpatient clinic.

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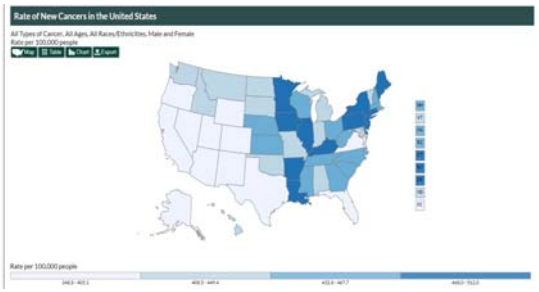
New Rates of Cancer in the US-2015



U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on November 2017 submission data (1999-2015): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; www.cdc.gov/cancer/dataviz, June 2018.

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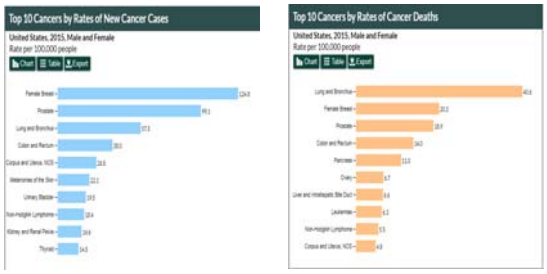
Top 10



U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on November 2017 submission data (1999-2015): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; www.cdc.gov/cancer/dataviz, June 2018.

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Relationship between diabetes and cancer

Prediabetes: 2014 meta-analysis found

Increased risk of:

- Liver (highest)
- Endometrial
- Stomach
- Colorectal
- Pancreas
- Breast

Not associated with:

- Bronchus/Lung
- Prostate
- Ovarian
- Kidney
- Bladder

Huang, Y, et al, Prediabetes and the risk of cancer: a meta-analysis. *Diabetologia* 2014 Nov 57(11) 2261-2269

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Type 1 Diabetes

Increased risk

Pancreatic

Liver

Esophageal

Colon

Increase mortality

non-Hodgkin's Lymphoma

Harding, J., et al. Cancer Risk Among People with Type 1 and Type 2 Diabetes: Disentangling True Associations, Detection Bias, and Reverse Causation *Diabetes Care* 2015 Feb; 38(2): 264-270

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Type 1 Diabetes

Increased risk women	Increased risk men
Rectal	Kidney
Stomach	
Thyroid	
Brain	
Lungs	
Endometrial	
Ovarian	

Harding, J., et al. Cancer Risk Among People with Type 1 and Type 2 Diabetes: Disentangling True Associations, Detection Bias, and Reverse Causation *Diabetes Care* 2015 Feb; 38(2): 264-270

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Type 2 Diabetes

Increased risk	Increased Mortality
Liver	Liver
Pancreas	Pancreas
Breast	
Colorectal	
Endometrial	
Gallbladder	

Harding, J., et al. Cancer Risk Among People with Type 1 and Type 2 Diabetes: Disentangling True Associations, Detection Bias, and Reverse Causation *Diabetes Care* 2015 Feb; 38(2): 264-270
Konstantinos, K, et al, Type 2 Diabetes and Cancer: umbrella review or meta-analyses of observational studies *BMJ* 2015 Jan;

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Type 2 Diabetes

Increased mortality based on sex
Gallbladder (females)

Stomach (females)

non-Hodgkin's lymphoma (females)

Did you know?
Women with diabetes have a 6% greater risk to developing cancer?

Harding, J., et al, Cancer Risk Among People with Type 1 and Type 2 Diabetes: Disentangling True Associations, Detection Bias, and Reverse Causation *Diabetes Care* 2015 Feb; 38(2): 264-270

Ohkuma, T, et al, Sex differences between the association between diabetes and cancer: a systematic review and meta-analysis of 121 cohorts including 20 million individuals and one million events *Diabetologia* 2018 July; 61:2140-2154

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Evaluation of glucose control

Hgb A1c

- Limited to those with a normal hematological profile.
- Is the patient anemic?
- Do they have a condition that will increase or decrease cell turnover?
  - Increased cell turn over will lead to artificially high levels
  - Decreased cell turn over will lead to artificially low levels
- Assess to see if they have received PRBC's in the past 90 day
  - Results with be artificially low if transfused.
  - Frequent transfusions in Leukemia and Lymphoma patients.

Wright, L, et al, Metrics Beyond Hemoglobin A1c in Diabetes Management: Time in Range, Hypoglycemia, and other Parameters *Diabetes Technology & Therapeutics* 2017 19 (2) S16-26

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Evaluation of glycemic control

Fructosamine

- Unaffected by RBC lifespan
- Protein dependent
- Monitor protein status
- Artificially elevated
  - Hypothyroidism or with cirrhosis
- Artificially lowered
  - Liver failure, low serum albumin level, nephrotic syndrome, hyperthyroidism, high triglyceride levels, nonalcoholic fatty liver disease

Wright, L, et al, Metrics Beyond Hemoglobin A1c in Diabetes Management: Time in Range, Hypoglycemia, and other Parameters *Diabetes Technology & Therapeutics* 2017 19 (2) S16-26

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Evaluation of glycemic control

Finger stick blood glucose monitoring

- ISO 15197:2013 requires 95% of test fall within +/-15 mg/dl for glucose less than 100 mg/dl and 15% for glucose readings over 100 mg/dl
- There is no systematic post market Surveillance Program for BGMS once cleared by the FDA.
- No studies have been conducted to see if chemotherapy affects readings
- New Surveillance Program is "intended to protect people with diabetes from inaccurate, poorly performing BGMS products" it will provide an "independent assessment of the analytical performance of BGMS following clearance from the FDA as well as to generate information that can assist people with diabetes, health care providers, and payers in making educated selection of BGMS".

Klonoff, D, et al, Development of the Diabetes Technology Society Blood Glucose Monitor System Surveillance Protocol *Journal of Diabetes Science and Technology 2016* 10 (3) 697-707

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Imaging

- PET Scans
  - No long acting insulin for 6 hours before testing
  - No short acting insulin for 4 hours before testing
  - Glucose must be under 200 mg/dl.
- MRI, CT and X-Ray
  - Must remove pumps and sensors
    - Per manufacturer recommendations
    - Please teach when doing training.
      - We had a patient from a Southern State that wore her pump into a MRI.

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Treatment Options

Chemotherapy

Immunotherapy

Stem Cell Transplant

Radiation

Surgery

CART

Often there will be a combination of the above therapies

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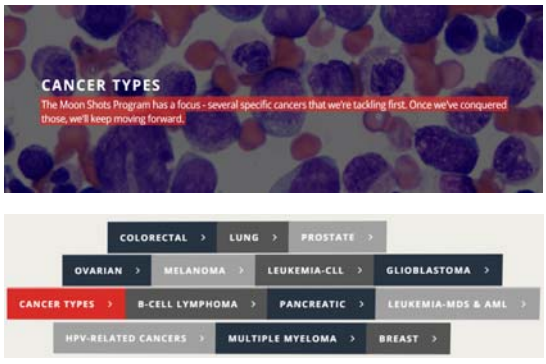

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Chemotherapy

Neoadjuvant therapy: used to shrink tumors before surgery or radiation

Adjuvant: to make sure all cancer cells have been eliminated after other treatments have been performed

Best practice is to review the complete individual treatment plan

There are many different and complex treatment options both with and without steroids.

Have you heard….

"Steroids won't affect your glucose…much"

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Half-Life of frequently used steroids

Steroid	Half-Life
Hydrocortisone	8-12 hours
Prednisone	16-22 hours
Methylprednisolone	18-36 hours
Dexamethasone	36-54 hours

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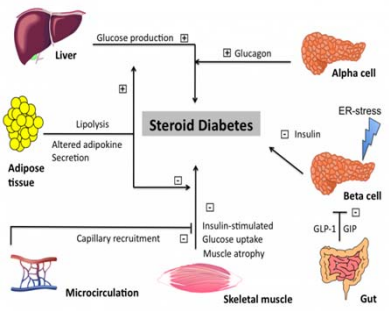
How steroids affect the glucose levels



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Chemotherapy Regimens

R-CHOP

- Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.
  - Prednisone 100-120 mg on days 1-5 of each cycle.

R-EPOCH

- Rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin.
  - Prednisone 100-120 mg on days 1-5 of each cycle.

Hyper CVAD

- Cyclophosphamide, Vincristine, Adriamycin and dexamethasone.
  - Dexamethasone on days 1-4 and 11-14 on odd cycles
- Rituximab weekly 21 day cycle
  - Dexamethasone 10 mg on days 1, 8, 15 and 21

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Chemotherapy Regimens- Just a few more

- BR OP: PACLitaxel Weekly
  - Dexamethasone 10 mg each week
- GI Colon OP: Irinotecan, 5-Fluorouracil, Leucovorin (Modified FOLFIRI) (18 cycles)
  - Dexamethasone 10 mg day 1 of each 14 day cycle.
- LEU OP+IP: TKI with Hyper-CVAD Regimen - Maintenance/Intensification
  - Prednisone 100 mg on days 1-5 of each cycle.
- LYM OP/IP: REDUCED DOSE Cyclophosphamide, DOXOrubicin, VinCRIStine and PrediSONE (Bolus) with RiTUXimab (MINI R-CHOP)
  - Prednisone 80 mg on days 1-5
- Palbociclib and Fulvestrant
  - No steroids

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Phases of Clinical Trials

Animal and/or laboratory studies

Phase I (First use on human subjects)

- 15-30 patients

Phase II

- Fewer than 100 patients

Phase III

- 100-1000 patients

FDA Approval

Phase IV- after approval.

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Examples of clinical trials

2015-0069 Lenalidomide and OBINutuzumab with CHOP -21 Day Cycle

- Methylprednisolone 80 mg on days 1, 8, 15 of each cycle

2015-0488 Enzalutamide and Weekly PACLitaxel - 7 Day Cycle

- Dexamethasone 4 mg on days 1 of each cycle

- MD Anderson conducts hundreds of studies

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Immunotherapy

- Immunotherapy works by stimulating the body's own immune system to fight cancer cells.

The cells can work too well causing autoimmune diseases

- Encephalitis
- Hormone gland problems
  - Thyroid, pituitary, adrenal and pancreas
- Colitis
- Pneumonitis
- Hepatitis
- Kidney failure and nephritis

Can cause Type 1 Diabetes with presentation of DKA at any time after the first dose is given.

- Check C-peptide with concurrent glucose; GAD-65 & Insulin autoantibodies

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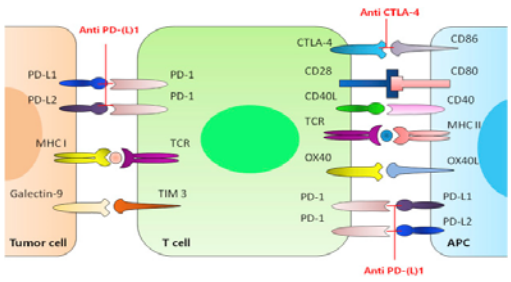
Immunotherapy



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Last Friday

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Immune checkpoint inhibitors

PDL-1 inhibitors

- Programmed Death-Ligand 1
  - Atezolizumab (Tecentriq)
  - Avelumab (Bavencio)
  - Durvalumab (Imfinzi)

PD-1 inhibitors

- Programmed Death Protein 1
  - Pembrolizumab (Keytruda)
  - Nivolumab (Opdivo)
  - Cemipilimab (Libtayo)

CTLA-4

- Cytotoxic T-Lymphocyte-associated protein 4
  - Ipilimumab

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Immune checkpoint inhibitors

P13K-AKI-mTOR inhibitors

Associated with 13-50% incidence of hyperglycemia/new onset diabetes

- Everolimus/Afinitor
- Temsirolimus/Torisel
- Sirolimus/Rapamune

Pi3K Inhibitor

Associated with hyperglycemia in 41-65%.

Copanlisib-Follicular Lymphoma

Alpelisib- HR + HER2 negative/negative breast

Idelalisib- refractory CLL/SLL; 3rd option after previous failure-FL * (no elevations on PI)

Duvelisib refractory CLL/SLL; 3rd option after previous failure-FL * (no elevations on PI)

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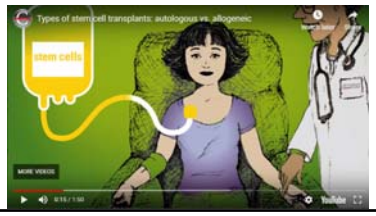
Stem Cell Transplant

- **Autologous**- Cells are collected from the patient's own bone marrow
  - Little to no risk of rejection or GVHD (Graft Vs Host Disease)
- **Allogenic**- Cells are collected from a donor
  - Haploidentical (related usually 1st degree relative)
  - Matched unrelated donor
  - Increased risk of rejection or GVHD



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Pretreatment course can be complex

- Example: BEAM with Rituximab
  - Day -6 Dexamethasone
  - Day -5 Hydrocortisone
  - Day -4 Hydrocortisone
  - Day -3 Hydrocortisone
  - Day -2 Hydrocortisone
  - Day -1 Dexamethasone
  - Day 0 Hydrocortisone 100 mg 30 minutes prior to transplant.

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Post-Transplant

- Decreased appetite and taste changes around day 4-5 post-transplant.
- Complications:
  - Increased bleeding
  - Anemia
  - Fatigue
  - Mouth sores
- Acute Graft Vs Host Disease
  - Can occur anywhere in the body.
    - Most frequently GI, Skin and Liver
    - Often will start on high dose steroids 2 mg/kg
- Chronic Graft Vs Host Disease
  - Can occur anywhere in the body.

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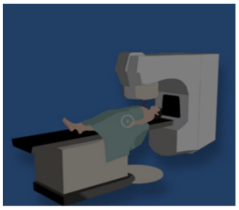
Radiation Therapy

- Used to decrease or destroy cancer cells
- Simulation used first
- Often requires multiple treatments
- Used alone or in combination with surgery and/or chemotherapy



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Surgery

- Preventive- used to keep cancer from occurring (aka prophylactic surgery)
- Staging- determines the extent of the cancer
- Curative- removal of all of a cancer
- Palliative- improves quality of life; not a cure
- Steroids are often given intraoperatively
- Pasireotide given with pancreatic surgery

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Chimeric Antigen Receptor T-Cell
CART

White blood cells (including T-Cells) are gathered through apheresis.

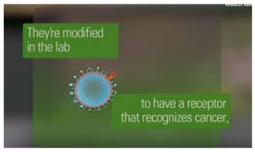
In the lab the T-cells are separated and new DNA is introduced in to the cell with a virus.

The new DNA causes a change to the receptors on the surface of the cell; they are now (CAR) T-cells.

The modified cells are allowed to multiply until there are millions of cells.

The modified cells are then infused back into the body.

The CART-cell receptors are attracted to the targets on the surface of cancer cells and kill the cancer cells.



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