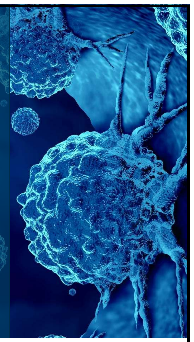


Modern Principles of Radiation Oncology

Yuan James Rao, MD
Assistant Professor of Radiation Oncology
Director of Brachytherapy
The George Washington University

GW ONCOLOGY UPDATE

Disclosures

- No disclosures reported

GW ONCOLOGY UPDATE

Outline

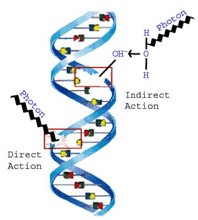
- Principles of Radiation Biology
- Technology of Radiation Oncology (Hardware)
- Treatment Planning in Radiation Oncology (Software)
- Selected Clinical Updates in Radiation Oncology

GW ONCOLOGY UPDATE

Principles of Radiation Biology

What is radiation and what does it do?

- Usually high energy photons, and occasionally other particles (electrons, protons, alpha particles)
- Photon energy in MV range (6 MV)
- Gray is the unit of radiation (J/Kg)
- **DNA damage**, particularly double strand breaks, is the primary mechanism of cell death after radiation



DNA damage: Double Strand Breaks

- **Lethal injury due to incorrectly repaired DNA damage**
  - Cells undergo mitotic catastrophe or apoptosis is triggered
- 1 Gy = ~40 double strand breaks in exposed cells

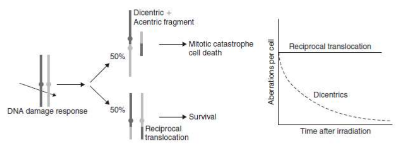
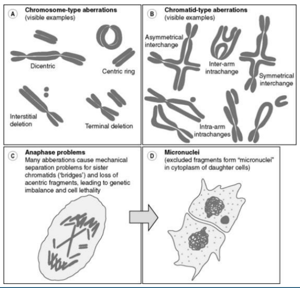


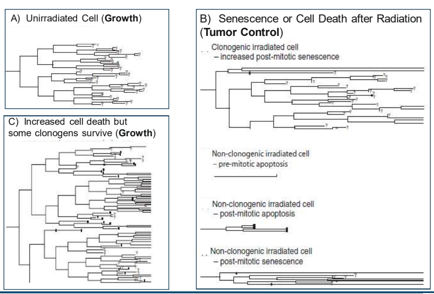
Figure 3.3 This figure, adapted from Brown and Attardi (2005), demonstrates the stochastic nature of cell death after irradiation. The DNA repair processes frequently lead to events in which chromosomes are not repaired correctly. It has been shown that irradiated cells produce approximately equal amounts of reciprocal translocations and dicentrics. The broken chromosomes in these cases are ligated to each other in a random or stochastic manner. Formation of a dicentric chromosome prevents proper mitosis and leads to cell death, whereas a reciprocal translocation that does not involve an important region of the genome is stable (sometimes for many decades).

Chromosome Aberrations after RT



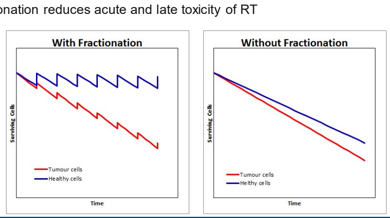
- **Lethal chromosome events:**
- **Pre-replication DNA:** Ring structures or Dicentric Chromosomes
- **Post-replication DNA:**
- Structures leading to Anaphase Bridges

Fate of Tumor Cells after RT



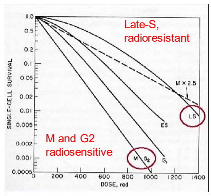
Fractionation in Radiation Oncology

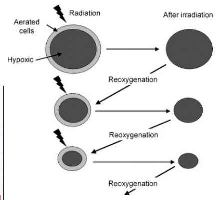
- Classically, radiation is delivered as daily treatments over several weeks
- This takes advantage of the differences between tumor and normal tissue in repairing DNA damage.
- This is called "Fractionation"
- In general, fractionation reduces acute and late toxicity of RT



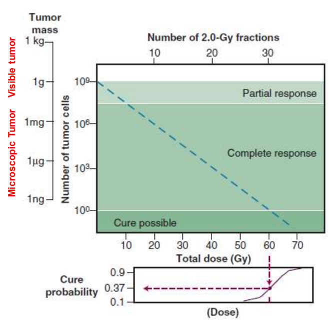
Fractionation in Radiation Oncology

- Fractionation also takes advantage of re-oxygenation of tumor cells, allowing for more effective treatment of hypoxic tumors, which are normally resistant to radiation.
- Fractionation also increases the likelihood that tumor cells are treated in more sensitive phases of the cell cycle (M and G2)





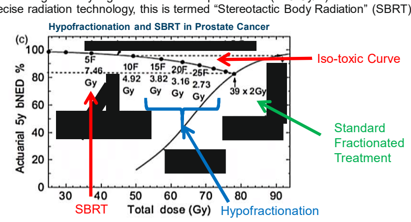
Fractionation allowing for re-oxygenation of a hypoxic tumor



- Radiation kills a proportion of tumor cells per treatment (log-kill).
- Cure is possible when <1 clonal cell remains.
- Probability of cure = e^(-N), where N is the probable number of remaining clonal cells, according to Poisson statistics.
- Probability of cure depends on radiation sensitivity, initial tumor mass, and radiation dose/fractions

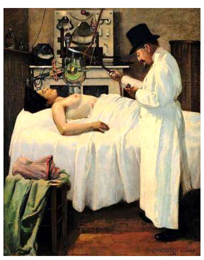
Hypofractionation and "Ultra-hypofractionation"

- Contrary to traditional fractionation principles, hypofractionation means giving larger dose per treatment in a fewer number of treatments.
- Can be safely accomplished using modern radiation technology, which exposes less normal tissue to radiation dose.
- "Ultra-hypofractionation" gives very high radiation doses per fraction (>=5 Gy/fx) in a few treatments. When delivered with precise radiation technology, this is termed "Stereotactic Body Radiation" (SBRT).



Technology of Radiation Oncology

Early Radiation (1895-1930)


Treatment of Breast Cancer, 1910

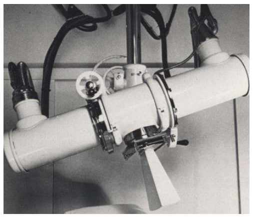
- **1895** – Röntgen discovers X-rays
- **1896** – Becquerel and Curie identify radioactive elements
- **1896** – First patients with cancer treated with x-rays by Emil Grubbe in Chicago
- Early XRT used low energy X-ray tubes

Early Radiation (1895-1930)

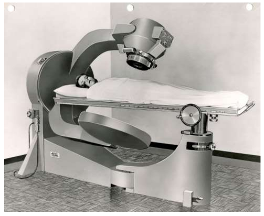

Treatment of Skin Cancer, 1915

- Early X-ray devices produced low energy Xrays with high skin dose but low penetration
- Useful for superficial tumors but less useful for deep tumors
- Difficult to treat pelvic tumors using this method

Early Radiation (1930-1950s)

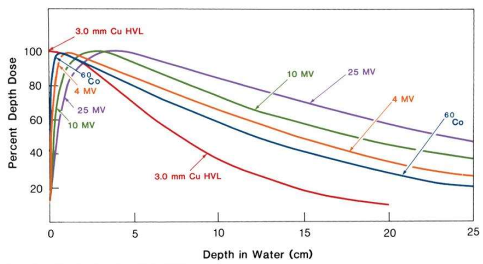


200 kV orthovoltage x-ray tube used for radiation therapy, 1938



Cobalt-60 Teletherapy Unit

Greater Energy = Greater Depth Dose



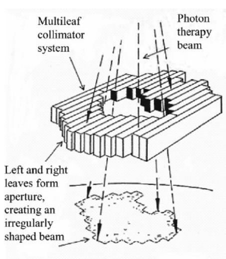
Linear Accelerator (1950s)

Gordon Isaacs, first patient treated with the linear accelerator

- Developed by Kaplan and Ginzton at Stanford
- Use of Klystron to accelerate electrons and generate high energy X-rays
- Able to produce X-rays in the megavoltage range
- Deeply penetrating with more skin sparing
- Modern Linacs can also deliver intensity modulated radiation (IMRT), which is useful for covering pelvic/abdominal tumors with low toxicity

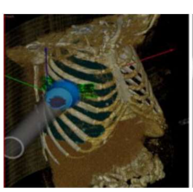
Linear Accelerator (TrueBeam) at George Washington University

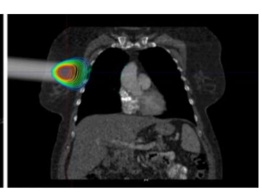
Multi-Leaf Collimator (Beam Shaping)



Electrons useful for superficial tumors

- Modern linear accelerators can also be set in "electron mode" which are useful for treating superficial tumors





Stereotactic Radiation

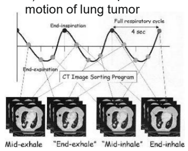
SBRT or SRS is less of a “technology” and more of a “process”

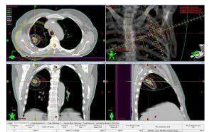
1. Ultra-hypofractionation – high doses/few fractions
2. Precise immobilization and motion management
3. Precise treatment planning
4. Treatment using a machine capable of precise delivery

Example of Lung SBRT Process

1) 50 Gy in 5 Fx → 2) 4D – CT to capture motion of lung tumor → 3) Treatment Planning

Ultra-hypofractionation!





SBRT or SRS Treatment Delivery

- After planning, treatment must be delivered on a machine capable of treating small targets.
- Several different modern machines are capable of SBRT/SRS delivery with similar clinical effectiveness

Example of Multi-Purpose SBRT Device

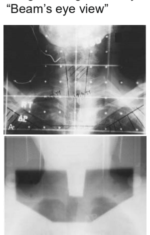
- “Gantry-based” SBRT
- Truebeam or Edge– Can be used for SBRT/SRS and conventional XRT or IMRT

Examples of Specialty SBRT/SRS Devices

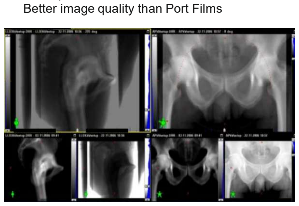
- Cyberknife – Robotic miniature Linac for SBRT or SRS
- Gammaknife – Specialized SRS device with Co60 Sources for brain treatment
- Zap-X – Specialized SRS with self-shielded miniature linac for brain treatment

Imaging in Radiation Oncology

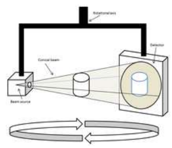
Port Films
Imaged using MV X-rays
“Beam’s eye view”

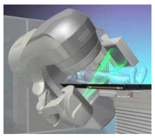


KV Imaging
Imaged using diagnostic quality KV Xrays
Usually AP and Lateral
Better image quality than Port Films

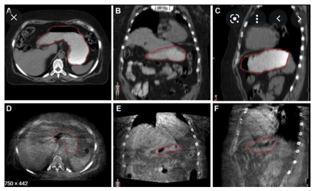


Imaging in Radiation Oncology





Cone Beam CT (CBCT)
Rotation of KV imager around patient
Computer reconstruction to create CT-like image
Excellent for verification of targeting
Standard of care for Image Guided Radiation (IGRT)



GW ONCOLOGY UPDATE

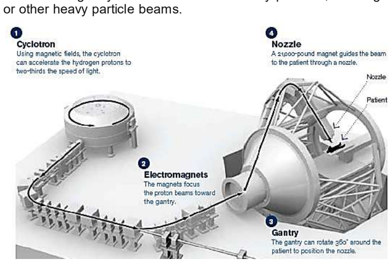
MRI Linear Accelerator

- Two commercially available devices have recently become available that incorporates MRI as the on-board imaging technology for the linear accelerator
  - ViewRay (0.3 Tesla Magnet)
  - Unity (1.5 Tesla Magnet)
- MRI imaging allows for better soft tissue definition during radiation
- Potential for better targeting of soft tissue lesions or mobile tumors (example: SBRT for mesenteric lymph node that moves each day)

GW ONCOLOGY UPDATE

Particle Therapy

- Particle therapy involves using a cyclotron to accelerate heavy particles, allowing for the production of neutron, proton, or other heavy particle beams.



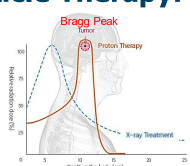
GW ONCOLOGY UPDATE

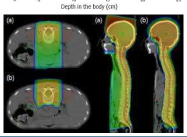
Particle Therapy: Neutrons

University of Washington
Medical Cyclotron Facility

- Neutrons are the oldest heavy particle investigated in Radiation Oncology
- Neutrons are thought to overcome tumor hypoxia
- However, was discovered to also cause significant normal tissue toxicity.
- Has only been demonstrated to be superior to conventional Xrays in a small trial of 32 patients with unresectable salivary gland tumors (Laramore et al, IJROBP, 1988)
- University of Washington operates the only clinical neutron facility in US

Particle Therapy: Protons





- Proton therapy takes advantage of the Bragg peak, in which dose is preferentially deposited at a certain depth along the beam path.
- Dosimetric advantages are observable, and likely most important for pediatric patients and re-irradiation cases.
- Pediatrics/Young Adults: Possibly reduce secondary malignancy due to low dose bath (not yet clinically proven)
- Toxicity: Some disease sites (esophagus) are nearly surrounded by radiation sensitive organs and there may be toxicity benefit in this setting
- Negative: Expense, Not widely available
- Understanding of proton physics and biology not as robust as with Xrays

Particle Therapy: Protons

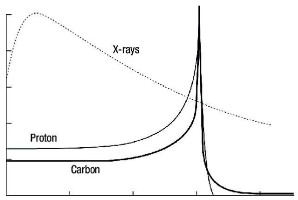
- Randomized trials are needed to test the efficacy of proton therapy vs standard of care treatment
- Currently, randomized trials exist for breast, brain, head and neck, lung, prostate, esophageal, hepatocellular carcinoma and others.
- To date, the only positive randomized trial for protons is in esophageal cancer, where proton therapy decreased toxicity vs IMRT (JCO 2021)
- Randomized trial of proton vs IMRT for prostate cancer has been open for 8 years and accrued 423/450 patients as of March 1, 2021. However, over the last decade >15,000 men with prostate cancer have been treated with proton therapy for prostate cancer off-trial in the US (PMID: 34171235)

Table A1. Current Status of Phase III Randomized Clinical Trials of Proton Therapy Versus Photon Therapy Funded by the National Cancer Institute and the Patient-Centered Outcomes Research Institute

ClinicalTrials.gov Registry Number	Disease Site	Primary End Point	No. of Months Active*	Enrollment of Total Sample Size*	No. of Proton Centers Enrolling*	Average Monthly Accrual, 6 Months*	Average Monthly Accrual, 12 Months*
NCT02603341	Breast cancer	Major cardiovascular events	23	317 of 1,716	20	19.0	17.4
NCT02179086	Glioblastoma	Overall survival	39	96 of 288†	16	3.5	3.2
NCT01993810	Lung cancer	Overall survival	47	101 of 330‡	10	0.7	1
NCT01617161	Prostate cancer	Patient reported bowel outcomes	62	254 of 400	12	4.3	5.1
NCT01512589	Esophageal carcinoma	Progression-free survival and total toxicity burden	69	126 of 180§	1	0.7	1.1
NCT03186898‖	Hepatocellular carcinoma	Overall survival	7	1 of 167	1	0.2	Not applicable
NCT03180502¶	Low-grade glioma	Preservation of neurocognition	6	1 of 120	7	0.2	Not applicable

*As of January 31, 2018.

Particle Therapy: Carbon/Helium

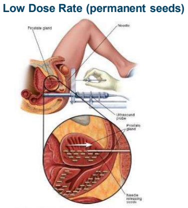


- "Hadron therapy"
- Heavier particles such as Carbon or Helium and others have a "sharper" Bragg peak and may have further dose advantages compared to proton therapy.
- Currently available in Europe and Japan but not in US
- Stanford University and Mayo are constructing first US facilities.

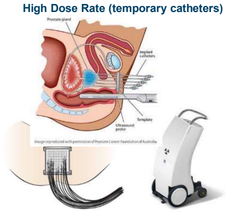
Brachytherapy

- Internal placement of radiation sources
- Effective treatment for prostate cancer, gyn cancers, and some other tumors (recurrent tumors, skin, H&N)

Prostate
Low Dose Rate (permanent seeds)

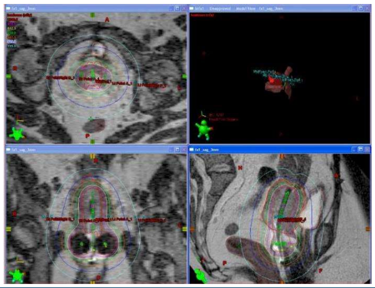


Prostate
High Dose Rate (temporary catheters)



Brachytherapy

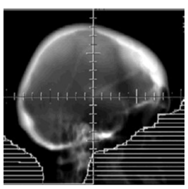
Example of MRI-Based Brachytherapy for Uterine Cervix Cancer



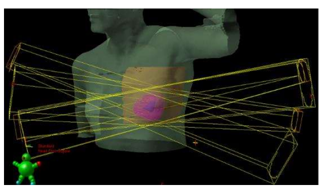
Treatment Planning in Radiation Oncology

2D and 3D Radiation Planning

2D Planning of Whole Brain Radiation

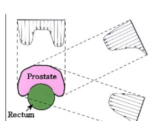


3D Conformal Planning of Breast Radiation

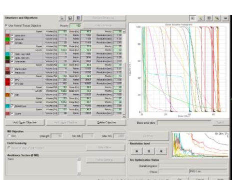


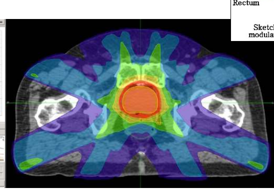
Intensity Modulated Radiation

- IMRT uses multiple beams or arcs of beams where beam modulation is optimized by a computer algorithm.
- Total dose is the summation of these modulated beams.
- Standard of care in H&N cancer, prostate cancer, and others

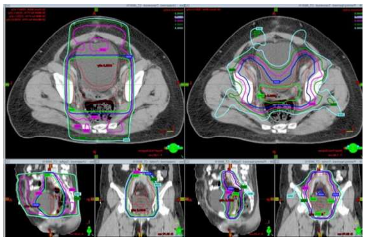


Sketch illustrating intensity modulated beams of radiation.





External Radiation Planning 3D Conformal vs IMRT

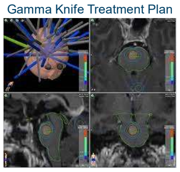


3D treatment (left) with 4 fields intersecting in a "box" IMRT treatment (right) with many intersecting fields conformal to target

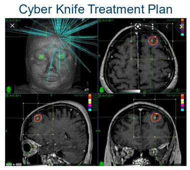
How is SBRT / SRS planned?

- Remember that SBRT is a process, not a particular treatment planning technology
- The underlying plan in the computer system for an SBRT treatment delivery can be IMRT or 3D-CRT
  - Most commonly IMRT for gantry-based systems such as TrueBeam.
  - Cyberknife and Gamma-knife have treatment planning systems that are more similar to 3D-CRT, although unique aspects of their delivery technology allow for very conformal plans

Gamma Knife Treatment Plan



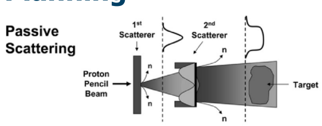
Cyber Knife Treatment Plan



Proton Treatment Planning

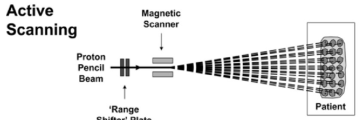
Passive Scatter

- Analogous to 3D-CRT for Protons



Intensity Modulated Proton Therapy (IMPT)

- Analogous to IMRT for Protons
- Often uses a narrow "Pencil Beam" that is moved around by magnets
- Some facilities capable of passive scatter but not IMPT



Selected Clinical Updates in Radiation Oncology

- Note: Focus on new information in radiation techniques and indications, rather than on combinations with systemic therapy that are likely well covered elsewhere.

SBRT for Oligometastasis

- Long term outcomes of SABR-COMET Phase II study (n=99) of SBRT vs standard of care for 1-5 oligometastasis recently published (JCO 2020)
- Improvement in OS at 5 years (42% vs 17%)

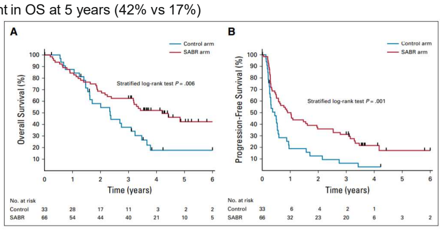
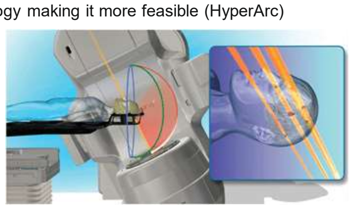


FIG 2. Kaplan-Meier plots for (A) overall survival and (B) progression-free survival. SABR, stereotactic ablative radiotherapy.

Advanced Technology Allows us to treat more brain mets

- Frequently infeasible to treat many metastases (>5) with SRS due to resource utilization and logistics
- New Technology making it more feasible (HyperArc)



Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study

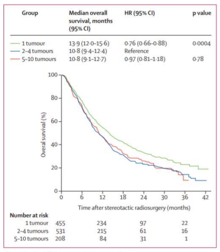


Figure: Kaplan-Meier curves of overall survival
HR=hazard ratio.

- Retrospective data suggests outcomes after SRS for 5-10 brain metastasis similar to that for 2-4 brain metastasis

Lancet Oncol 2014; 15: 387–95

Where are we going?

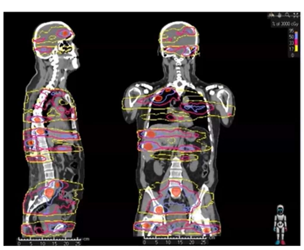
Number of Metastases	1	4	10
	SABR-COMET-3 Phase III	SABR-COMET-10 Phase III	ARREST Phase I
	Stereotactic ablative radiotherapy for the comprehensive treatment of 1-3 Oligometastatic tumors (SABR-COMET-3): study protocol for a randomized phase III trial BMC Cancer 2019	Stereotactic ablative radiotherapy for the comprehensive treatment of 4–10 oligometastatic tumors (SABR-COMET-10): study protocol for a randomized phase III trial BMC Cancer 2019	EDITORIAL Beyond Oligometastases IJROBP 2020
	1-3 Metastasis	4-10 Metastasis	Unlimited!

Slides/Figures from Palma ASTRO 2020

SBRT for poly-metastatic disease

- Phase 1 “ARREST” clinical trial currently ongoing in Canada

Ablative
Radiotherapy to
Restrain
Everything
Safely
Treatable

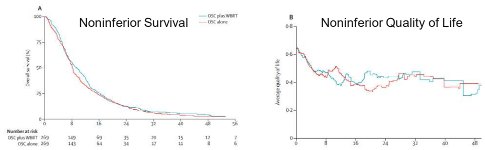


Slides/Figures from Palma ASTRO 2020

Omitting WBRT is reasonable for older patients with poor prognosis primary tumors

Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial

Eligible patients had brain mets from lung cancer and not eligible for surgery or stereotactic RT, and clinician/patient uncertainty about benefit of WBRT



Lancet 2016; 388: 2004-14

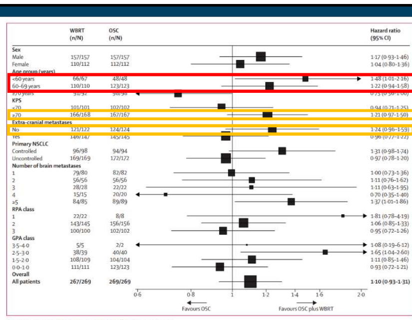


Figure 3: **Forest plot of overall survival by patient characteristics**
All hazard ratios are obtained from Cox proportional hazard models with adjustment for randomised group only. KPS=Karnofsky Performance Status. NSCLC=non-small cell lung cancer. RPA=recursive partitioning analysis. GPA=graded prognostic assessment. WBRT=whole brain radiotherapy. OSC=optimal supportive care.

Volume De-escalation in H&N Cancer

Limiting Radiotherapy to the Contralateral Retropharyngeal and High Level II Lymph Nodes in Head and Neck Squamous Cell Carcinoma is Safe and Improves Quality of Life (Cancer, 2014)

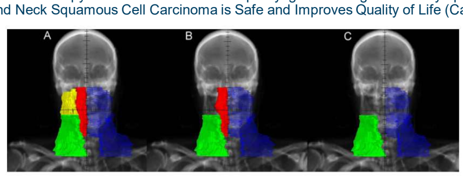


Figure 1.
AP radiograph demonstrating CTV elective nodal volume contours. In blue is the ipsilateral neck. Green represents the contralateral low neck, below level where the posterior belly of the digastric muscle crosses the internal jugular vein. Yellow indicates the contralateral high level II and red the contralateral retropharyngeal lymph nodes. (A) Generation 1. (B) Generation 2. (C) Generation 3.

Volume De-escalation in H&N Cancer

- In most cases it is not necessary to give postoperative radiation to the dissected pN0 neck (Contreras, JCO, 2019)

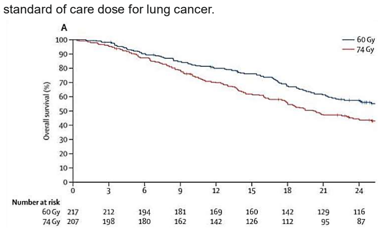
Eliminating Postoperative Radiation to the Pathologically Node-Negative Neck: Long-Term Results of a Prospective Phase II Study

Jessika A. Contreras, MD[1]; Christopher Spencer, MD, MS[1]; Todd DeWees, PhD[2]; Bruce Haughey, MD[3,4]; Lauren E. Henke, MD, MSCI[1]; Re-I Chin, MD[1]; Randal Paniello, MD[1]; Jason Rich, MD[1]; Ryan Jackson, MD[1]; Peter Oppelt, MD[1]; Patrik Pipkorn, MD[1]; Jose Zevallos, MD, MPH[1]; Rebecca Chernock, MD[1]; Brian Nussenbaum, MD, MHCM[5]; Mackenzie Daly, MD[1]; Hiram Gay, MD[1]; Douglas Adkins, MD[1]; and Wade Thorstad, MD[1]

- Phase II study, 72 patients, any necks (ipsilateral or contralateral) that were dissected and pN0 were not radiated. pN+ necks and primary site were always radiated.
- 97% local nodal control in the unirradiated necks

Definitive Radiation Dose in Lung Cancer

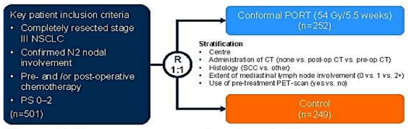
- RTOG 0617 compared 74 vs 60 Gy IMRT chemoradiation as definitive treatment of lung cancer. (Lancet Oncol, 2015)
- No benefit to 74 Gy, and may have been survival detriment.
- 60 Gy remains standard of care dose for lung cancer.



PORT for N2 NSCLC: Lung-ART

LBA3: An international randomized trial, comparing post-operative conformal radiotherapy (PORT) to no PORT, in patients with completely resected non-small cell lung cancer (NSCLC) and mediastinal N2 involvement. Primary end-point analysis of Lung ART (IFCT-0503, UK NCRI, SAKK) NCT00410683 – Le Pechoux C, et al

- **Study objective**
  - To assess the efficacy and safety of post-operative conformal radiotherapy (PORT) in patients with completely resected pN2 NSCLC



Primary endpoint
- DFS

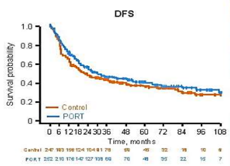
Secondary endpoints
- OS, patterns of relapse, local failure, second cancers, safety

Le Pechoux C, et al. Ann Oncol 2020;31(suppl):Abstr LBA3

PORT for N2 NSCLC: Lung-ART

LBA3: An international randomized trial, comparing post-operative conformal radiotherapy (PORT) to no PORT, in patients with completely resected non-small cell lung cancer (NSCLC) and mediastinal N2 involvement. Primary end-point analysis of Lung ART (IFCT-0503, UK NCRI, SAKK) NCT00410683 – Le Pechoux C, et al

- **Key results**



	Control	PORT
Median DFS, months (95%CI)	22.8 (17, 37)	30.5 (24, 49)
HR (95%CI)	0.58 (0.67, 1.07); p=0.16	
3-year DFS, % (95%CI)	43.8 (37, 51)	47.1 (40, 54)

DFS components (first event), n (%)	Control	PORT
All DFS events	152	144
Mediastinal relapse	70 (46.1)	36 (25.0)
Brain metastases	27 (17.8)	34 (23.6)
Other metastases	71 (46.7)	71 (49.3)
Death	8 (5.3)	21 (14.6)

Also no difference in OS

Le Pechoux C, et al. Ann Oncol 2020;31(suppl):Abstr LBA3

GW ONCOLOGY UPDATE

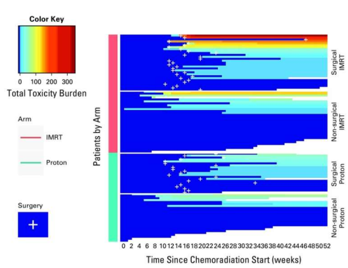
Definitive CRT Dose for Esophageal Cancer – ARTDECO Phase III trial

- 50.4 Gy vs 61.6 Gy IMRT (n=260) with concurrent carbo/taxol as definitive treatment for esophageal cancer (JCO 2021)
- The 3-year local progression-free survival (LPFS) was 70% in the SD arm versus 73% in the HD arm (not significant).
- The absence of a dose effect was observed in both adenocarcinoma and squamous cell carcinoma.
- ~50 Gy remains the standard radiation dose

GW ONCOLOGY UPDATE

Proton therapy vs IMRT for esophageal cancer

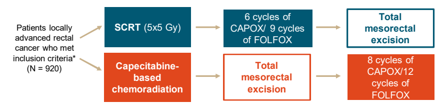
- 145 patients at MDA randomly assigned to PBT vs IMRT (50.4 Gy) as pre-operative or definitive therapy for esophageal cancer. (JCO 2020)
- A composite total toxicity burden (TTB) index was used and this was improved with PBT vs IMRT.



GW ONCOLOGY UPDATE

RAPIDO: Preoperative Short-Course Radiotherapy and Chemotherapy for Locally Advanced Rectal Cancer

- Randomized, international, multicenter phase III trial



*Inclusion criteria: biopsy-proven primary adenocarcinoma of the rectum, 18 years or older, absence of distant metastases, MRI with high-risk features (T4a/b, extramural vascular invasion +N2, mesorectal fascia + enlarged lymph nodes).

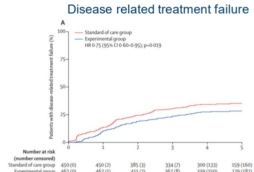
- Primary endpoints: disease-related treatment failure
- Secondary endpoints: OS, R0 rate, pCR, toxicity, surgical complications, QoL at 3 yrs

Slides/Figures from Hospers ASCO 2020

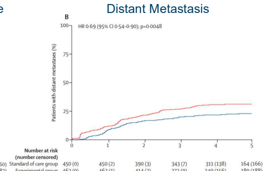
RAPIDO

- Experimental treatment reduced the risk of disease related treatment failure, particularly distant metastasis.
- Total neoadjuvant treatment strategy is often preferable, and a short course of radiation (25 Gy in 5 fx) is a feasible component of this strategy.

Disease related treatment failure

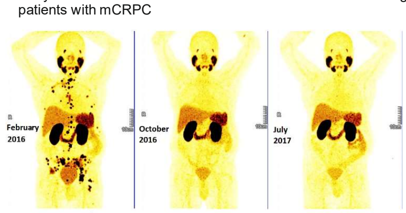


Distant Metastasis

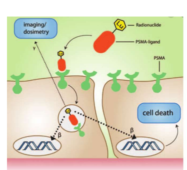


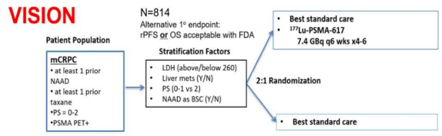
Radiopharmaceuticals – Lu 177-PSMA

- Lu177 is a beta emitting radioisotope, that can be bound to a protein using a chelator and linker
- Early clinical studies of Lu-PSMA have identified dramatic imaging and PSA responses in patients with mCRPC

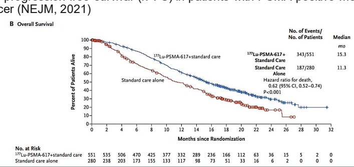


PSA 356.2 ng/ml PSA 0.00 ng/ml PSA 0.00 ng/ml





- Phase III VISION study with 177Lu-PSMA-617 met both primary endpoints, significantly improving overall survival (OS) and radiographic progression-free survival (rPFS) in patients with PSMA-positive metastatic castration-resistant prostate cancer (NEJM, 2021)



GW ONCOLOGY UPDATE

Thank You!

GW ONCOLOGY UPDATE