Serial 4DCT/4DPET imaging to predict and monitor response for locally-advanced non-small cell lung cancer chemo-radiotherapy

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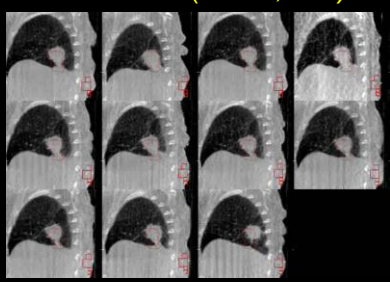
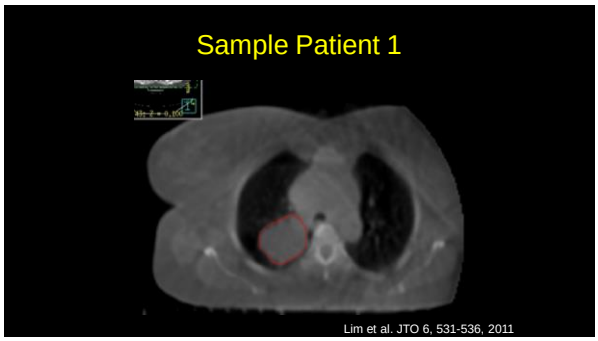
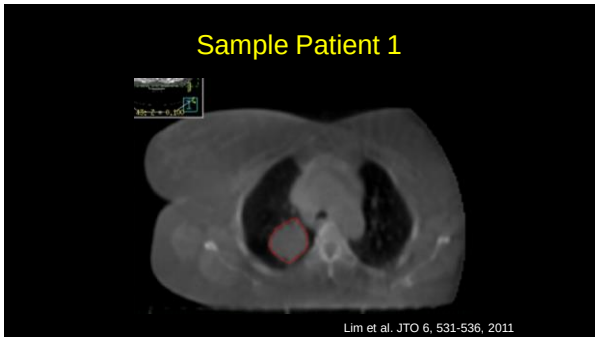
Why is Lung Cancer of Interest to Physicists?

- Target subject to physiological motions
  - Breathing ("regular" motion)
  - Coughing, discomfort (irregular motion)
- Difficult to deliver high, tumoricidal doses without increasing normal tissue complications
- Many patients have co-morbidities (other lung & heart disease)
- Low survival rates – deserves attention.

"5D" CBCT (*Sonke, NKI*)




Sample Patient 1
Lim et al. JTO 6, 531-536, 2011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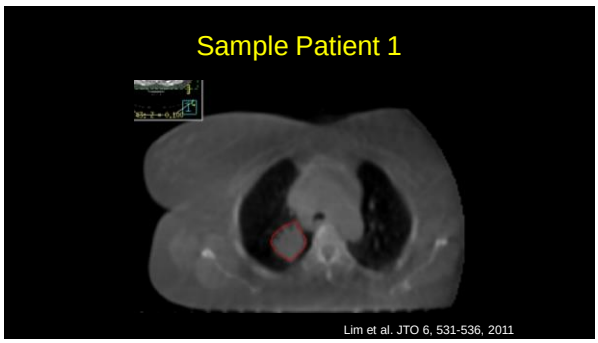
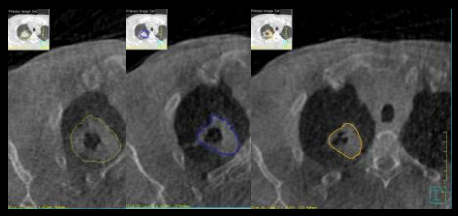

Sample Patient 1
Lim et al. JTO 6, 531-536, 2011

Sample Patient 2



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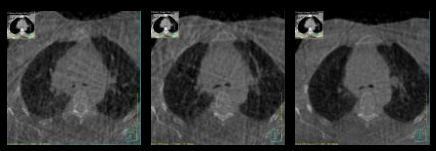
Sample Patient 3 - difficulties



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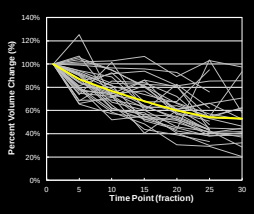
Monitoring Tumor Response with CBCT

- CBCT image quality is insufficient
  - Only 50% of primary tumours can be contoured
  - Nodal disease cannot be seen on CBCT
- Tumor volume increases in 1/6 pts!!!
- 14/31 had a shift in centre-of-mass coordinates ($p < 0.05$)



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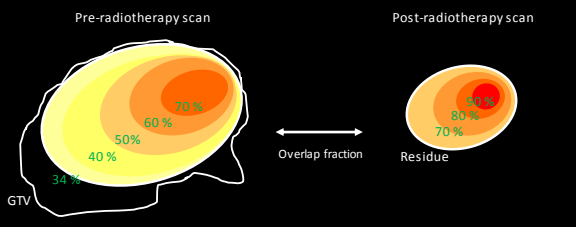
Findings from serial rcCBCT

- CBCT can tell us that variations occur, but not precisely
- Need higher quality images to monitor tumor response and perhaps intervene.
- Repeat 4DCT? PET imaging? ~~MR???~~

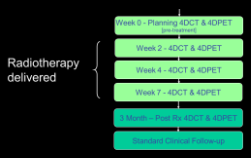
PET Imaging for Lung Cancer



Courtesy A. Dekker

Investigation

- Monitor tumor response using 4DCT, 4DPET
  - Identify responders from non-responders
  - Identify radio-resistant parts of the tumor with PET
  - Justify and evaluate replanning and boosting to transform non-responders to responders



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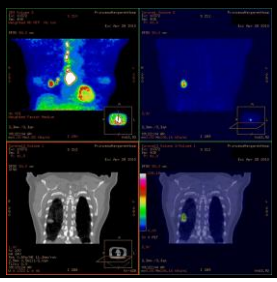
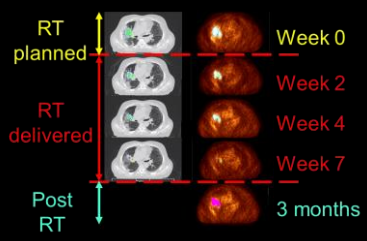
4D PET/CT



Monitoring Response to Treatment



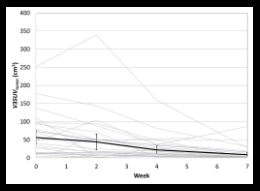
FDG-PET/CT Image Analysis

- Identified features from the literature
- Extract 4DCT and 4DPET features for each time point
  - 4DCT contours by experienced radiation oncologist
  - 4DPET volumes obtained from automatic contouring and analysis of Intensity Volume Histograms
- Calculate rate of change of these features with time.

Feature	Definition
$\#SUV_{nodes}$	Volume containing voxels with SUV ≥ 3 within the primary tumor
$V_{SUV_{nodes}}$	Volume containing voxels with SUV ≥ 3 within the nodal volume
$V_{SUV_{all\ diseased\ areas}}$	Volume containing voxels with SUV ≥ 3 within all diseased areas
$SUV_{peak,\ tumor}$	95th percentile of the SUV distribution within the primary tumor
$SUV_{peak,\ nodes}$	95th percentile of the SUV distribution within the nodal volume
$SUV_{50\%,\ tumor}$	Volume with a SUV ≥ 0.5 x $SUV_{max,\ tumor}$
$SUV_{50\%,\ nodes}$	Volume with a SUV ≥ 0.5 x $SUV_{max,\ nodes}$
$4TV_{tumor}$	Volume of the primary tumor as contoured on 4DCT
$4TV_{nodes}$	Volume of the affected lymph nodes as contoured on 4DCT

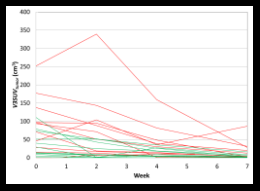
Materials and Methods: Image Analysis

- Build time trend for each patient.



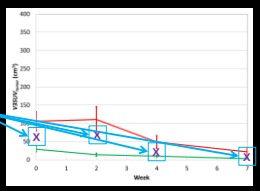
Materials and Methods: Image Analysis

- Build time trend for each patient.
- Dichotomize according to outcome 2 years post-RT.



Materials and Methods: Image Analysis

- Assess for statistical significance using Mann-Whitney, and log-rank tests.
- Identify optimal cut-offs using recursive partitioning method. (Breiman, 1984)
- Perform Kaplan-Meier survival statistics



Focus on dichotomized trends with $p < 0.005$

Feature	Week 0					Week 2					Week 4					Week 7				
	OS	PFS	LRFS	LRRFS	DRFS	OS	PFS	LRFS	LRRFS	DRFS	OS	PFS	LRFS	LRRFS	DRFS	OS	PFS	LRFS	LRRFS	DRFS
$V35UV_{tumor}$	-	0.006	<0.001	<0.001	-	-	0.007	<0.001	<0.001	-	-	0.001	<0.001	<0.001	-	-	-	-	0.034	-
$V35UV_{nodes}$	-	0.038	-	-	-	0.018	.023	-	-	0.047	0.017	0.004	-	-	-	-	-	-	-	-
$V35UV_{tumor + nodes}$	-	<0.001	<0.001	<0.001	-	0.023	<0.001	<0.001	<0.001	0.022	0.023	<0.001	<0.001	<0.001	0.021	-	-	-	0.019	-
$SUV_{peak, tumor}$	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
$SUV_{peak, nodes}$	-	-	-	-	-	-	0.042	-	0.018		-	0.006		0.003		-	0.041	-	0.032	
GTV_{tumor}	-	0.018	0.005	<0.001	-		0.005	<0.001	<0.001	-	-	0.009	0.003	<0.001	-	-	0.030	0.011	<0.001	-
GTV_{nodes}	-	0.037	-	-	0.038	0.003	0.001	-	-	<0.001	0.003	0.001	-	<0.001	-	0.025	0.005	-	-	0.005
$SUV_{50\%, tumor}$	-	0.029	0.021	0.0237	-	-	-	-	0.009	-	-	-	-	-	-	-	-	-	-	-
$SUV_{50\%, nodes}$	-	0.004	-	-	0.028	-	-	-	0.009	-	-	-	-	-	-	-	-	-	-	-

- Image features correlate better with PFS, LRFS, and LRRFS
- Some nodal features correlate with DRFS

Bissonnette et al. Radiother. Oncol. 126, 347-54 (2018)

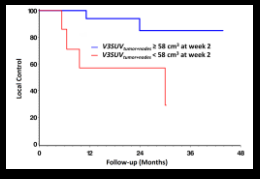
Optimal cut-offs with $p < 0.005$

Feature	Week 0					Week 2					Week 4					Week 7				
	OS	PFS	LRFS	LRRFS	DRFS	OS	PFS	LRFS	LRRFS	DRFS	OS	PFS	LRFS	LRRFS	DRFS	OS	PFS	LRFS	LRRFS	DRFS
$V35UV_{tumor}$	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
$V35UV_{nodes}$	-	-	-	-	-	-	-	-	-	-	-	1 cm^3	-	-	-	-	-	-	-	-
$V35UV_{tumor + nodes}$	-	87 cm^3	94 cm^3	87 cm^3	-	-	-	58 cm^3	58 cm^3	-	-	30 cm^3	32 cm^3	-	32 cm^3	-	-	-	-	-
$SUV_{peak, tumor}$	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
$SUV_{peak, nodes}$	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
GTV_{tumor}	-	-	-	-	-	-	-	64 cm^3	64 cm^3	-	-	-	55 cm^3	55 cm^3	-	-	-	-	47 cm^3	36 cm^3	-
GTV_{nodes}	-	-	-	-	-	-	-	-	-	-	26 cm^3	-	-	-	-	-	-	-	-	-
$SUV_{50\%, tumor}$	-	11 cm^3	-	16 cm^3	11 cm^3	-	-	-	9 cm^3	-	-	-	-	-	-	-	-	-	-	-
$SUV_{50\%, nodes}$	-	10 cm^3	-	-	10 cm^3	-	-	-	14 cm^3	-	-	-	-	-	-	-	-	-	-	-

- Combined (tumor + nodes) ^{18}F-FDG PET volumes < 94 cm^3 are more likely to achieve local control ($p < 0.005$)
- CT volumes do not correlate as strongly ($0.05 < p < 0.01$)

Kaplan-Meier statistics

- Analysis performed for all features and time points
- Favorable features indicate outcomes advantage
  - 37% higher chance of local relapse-free survival at 1 year, and 28% higher chance at 2 years



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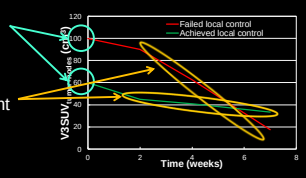
Typical trends with prognostic value

- Large vs. small initial volumes
- Large vs. small rate of change late in treatment



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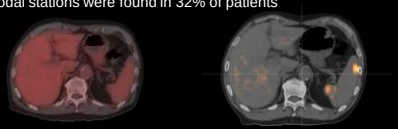
PET imaging and Lung Cancer RT

- The available evidence demonstrates substantial benefits for the use PET-CT for radiotherapy dose planning in NSCLC.
- Improvements target volume delineation
- Patient selection
- Change in treatment intent from radical to palliative in a significant proportion of patients.

Upstaging of disease is a concern because of the time lapse between diagnostic imaging and commencement of radiotherapy.

Disease Progression

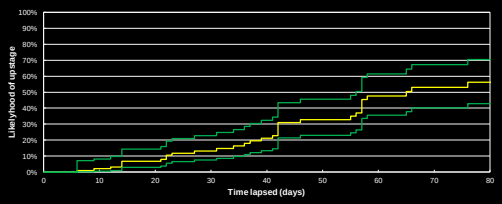
- Median time between diagnostic and treatment planning PET imaging: 21 days (average: 24.6 days)
- Overall, 25% of patients were upstaged; 7% in T, 14% in N, and 11% in M.
- New nodal stations were found in 32% of patients



July 20th August 31st

Biopsy proven metastatic deposit in Spleen

Predictive model for overall staging PM + Peter Mac + UPENN data (N=99)



Looking to pool data from NKI.

Pooled PM, Peter Mac, and UPENN data

	Time lapsed between staging PET and 1st RT treatment (days)					
	10	20	30	40	60	80
Probability of upstage in T	0%	2%	4%	4%	7%	7%
Probability of upstage in N	3%	6%	11%	18%	27%	47%
Probability of upstage in M	0%	5%	8%	8%	26%	32%
Probability of overall upstage	2%	7%	13%	21%	48%	56%

Wait time distribution 2012-2017 (Cancer Care Ontario, NSCLC)

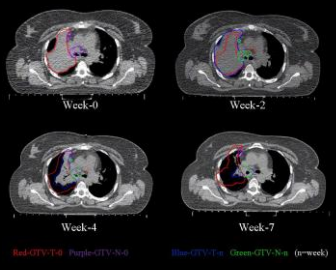
Treatment Received (First Treatment)	Number of Cases	Wait Time (in days) between PET Scan and radical treatment (for patients who received treatment within 3 months after PET Scan)					
All Patients (Patient with Single/Multi Primaries)		Minimum	10 Percentile	25 percentile	Median	Average	75 Percentile
Radiation Only	3521	1	17	28	42	44.7	62
Radiation and Chemo(Chemo)	573	1	9	19	32	35.1	49
Radiation and Chemo(Radiation)	295	1	11	20	36	38.2	53
Radiation and Chemo(Rads & Chemo)	1019	3	17	25	39	41.5	55

Should anticipate an overall upstage rate of ~22%, and ~8% upstage in M

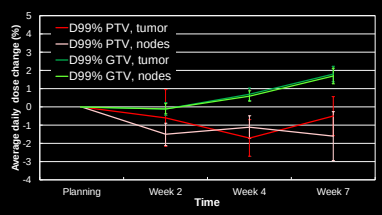
Adaptive Planning

- Groundwork for adaptive RT
  - Is it clinically feasible using current tools?
  - What is the best time to adapt?
- Examine two approaches:
  1. Recalculate plan on serial images
  2. Adapt therapy
     - Design a concurrent boost on "radioresistant" subvolume

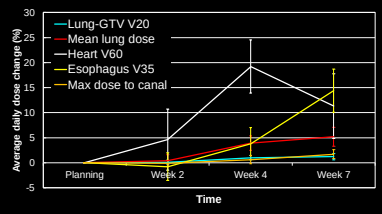
Recalculating the clinical plan



Fractional Dose to Targets



Fractional dose changes to OARs



Estimated Impact on Total Dose

Dose metric	Average change to total dose (%)
D99% GTV, tumor	0,7±0,3
D99% GTV, nodes	0,6±0,3
D99% PTV, tumor	-0,9±1,0
D99% PTV, nodes	-1,2±0,7
Max dose to canal	1,2±0,7
Lung V20	0,7±0,4
Mean lung dose	2,8±1,3
Heart V60	11,2±5,1
Esophagus V35	4,7±3,0

Metabolically-Adaptive Approach

- Boost dose to volumes of high metabolic activity (i.e., $SUV_{50\%}$), where recurrence is likely
- Plan with a concurrent boost to $SUV_{50\%}$ with dose as high as possible
- Don't exceed accepted toxicity thresholds (RTOG 0617)
- Simulate adaption with boost at week 0, 2 or 4

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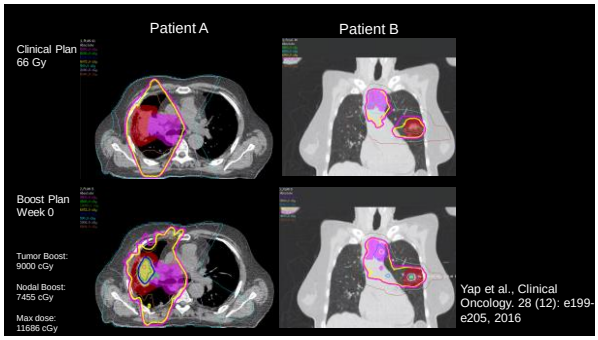

Yap et al., Clinical Oncology. 28 (12): e199-e205, 2016

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