ANADOLU

In Affiliation with
JOHNS HOPKINS MEDICINE

OFFLINE ADAPTIVE RADIOTHERAPY

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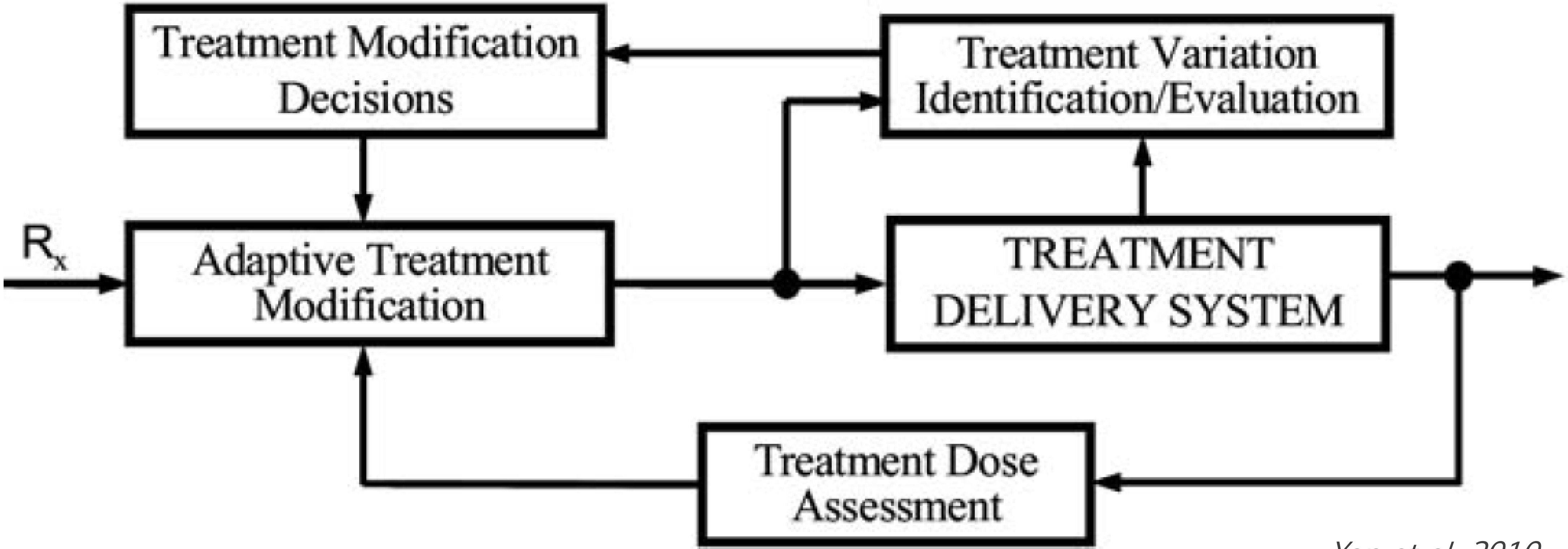
OVERVIEW

- Is there a need for adaptation?
  - Clinical rationale
  - Head and neck
  - Lung
- The workflow
- The uncertainties
  - Deformable registration (DIR)
- Cost / benefit
- How do we do it?

GENERAL INFORMATION

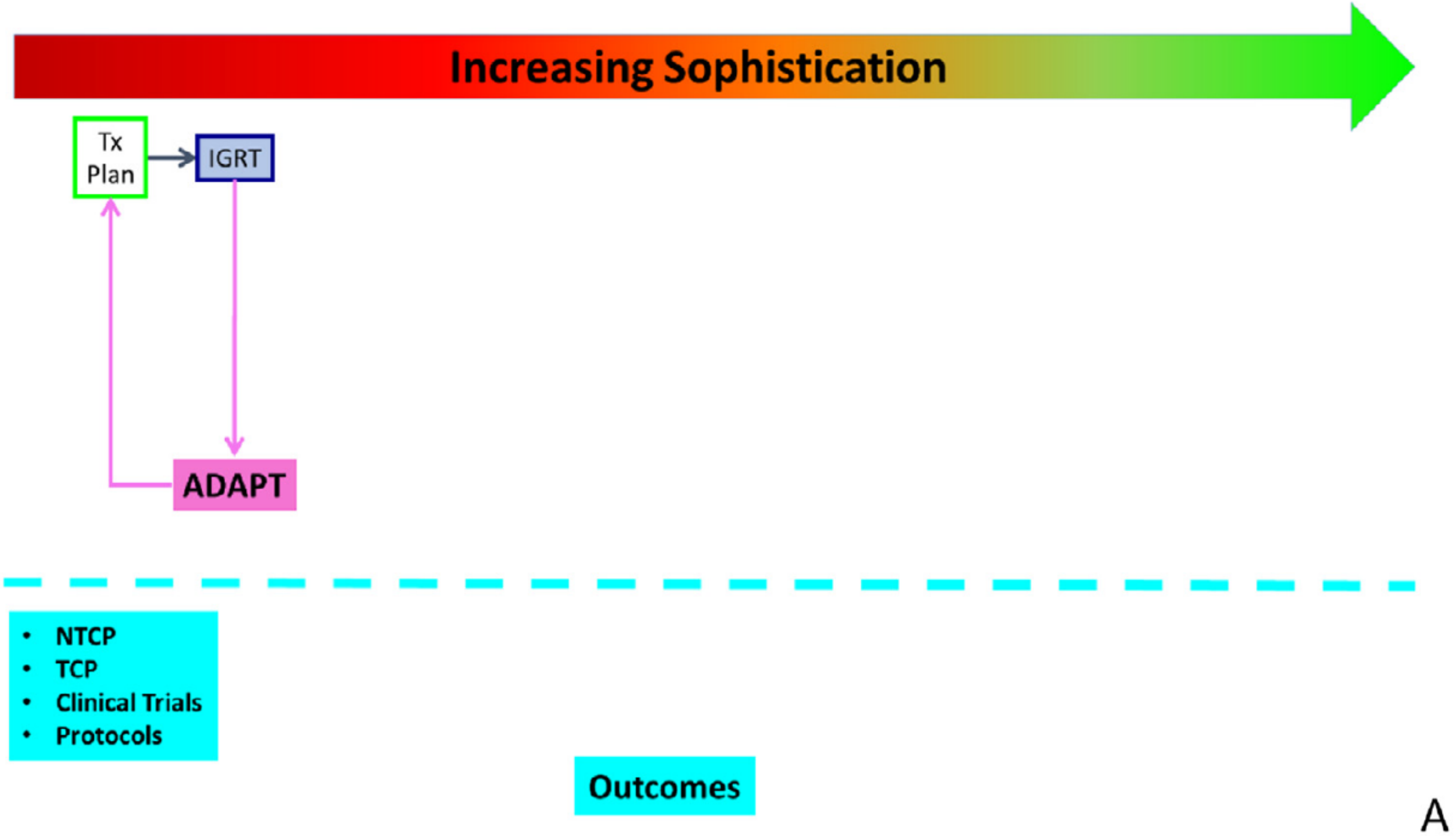
- Important role in cancer management
- Improvement is impeded by variability
  - Dosimetric variation by daily set up error
  - Radiation beam placement error
  - Changes of patient anatomical position, shape, and volume (weight loss, tumor response)
  - Biological variation throughout the treatment (the information from the PET images)

ADAPTIVE RADIOTHERAPY



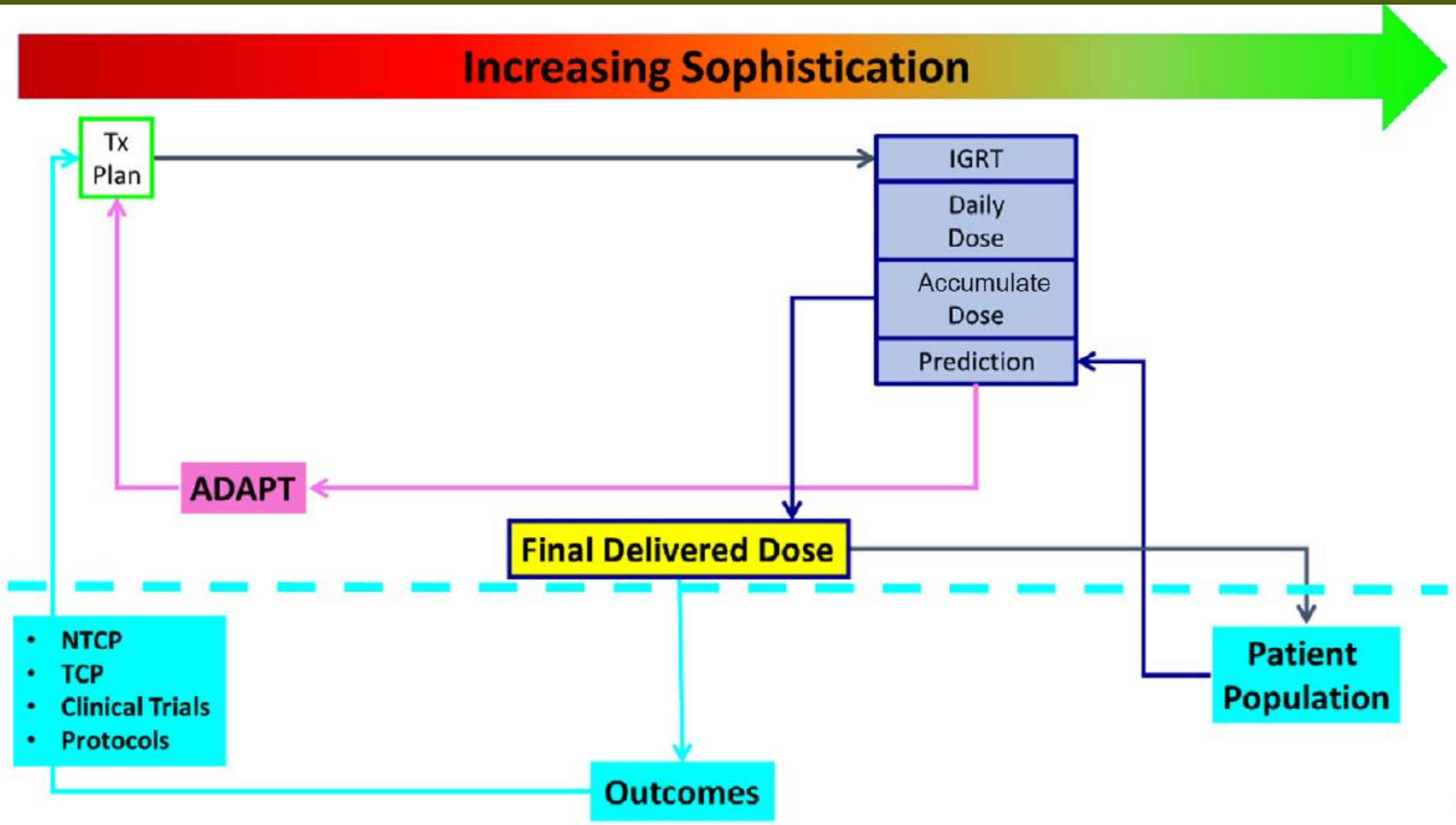
Yan et al, 2010

EVOLUTION OF ADAPTATION



Brook et al, 2019

EVOLUTION OF ADAPTATION



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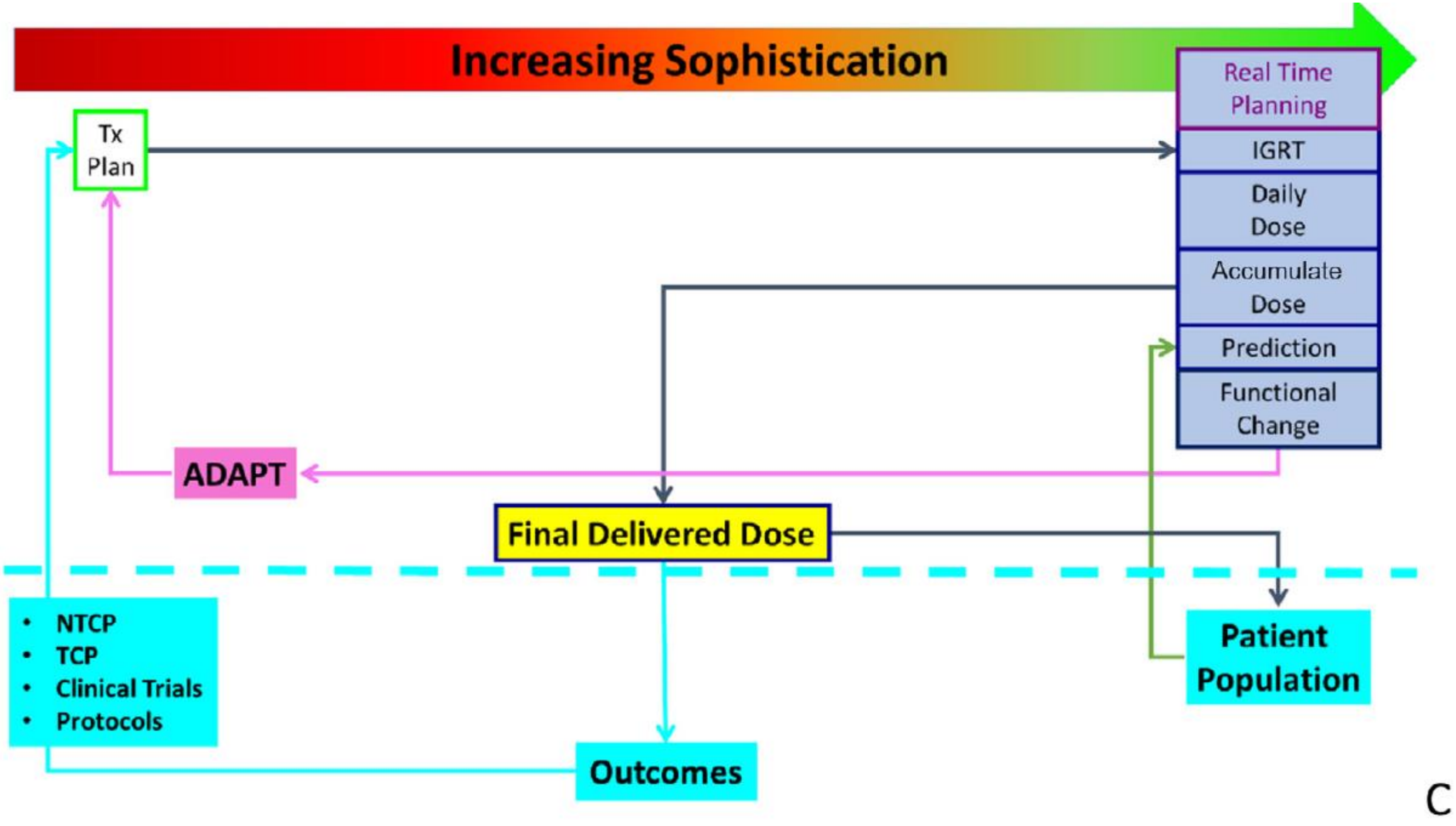
Brook et al, 2019

EVOLUTION OF ADAPTATION



Brook et al, 2019

ARTIFICIAL INTELLIGENCE (AI)

- To decrease the workload
  - Contouring
  - Registration
  - Planning
  - Quality assurance (QA)
  - Decision-making
- Objective
- Time consuming
- To change impossible into probable

CLINICAL PRACTICE - RATIONALE

- Clinical implementation is complex
- Requires fundamental shift of the infrastructure
- No level I evidence to prove the benefit
- No international guidelines
- Clinical data
  - Head-and-neck cancer
  - Lung cancer
  - Cervical cancer
  - Liver cancer
  - Bladder cancer
  - Prostate cancer

ART IN HEAD AND NECK CANCER

- Standard of care in organ sparing treatment
- 7-week period
- Major anatomical changes (weight loss, parotid / tumor shrinkage)
- Under / over dosage of target and OAR
- With the advent of 3D serial imaging
- Customized planning throughout the treatment
- Daily set-up accuracy

ART IN HEAD AND NECK CANCER

Table 1 Clinical Benefits of ART in Patients With Head and Neck Cancer

Author (year)	Nb Patients		Tumor site	Total dose (Gy)	Replanning Strategies		Clinical Endpoint			
	ART	No ART			Nb	Timing	Follow-Up (months)	Loco-regional Control and Survival	Acute Toxicity	Late Toxicity
Schwartz et al[11,*]	22	0	OPC	66-70	1 or 2	16th and 22th fr	31	2-year LRC = 95%	G III mucosal = 100% G II xerostomia = 55% G III xerostomia = 5%	Full preservation or functional recovery of speech and eating at 20 months
Kataria et al[69]	36	0	LAHNC	70	1	54 Gy		2-year DFS = 72% 2-year OS = 75%	G II-III mucosal = 100%	G II xerostomia= 8% G II mucosal = 11% No G III
Yang et al[70,*]	86	43	NPC	70-76	1 or 2	15th and/or 25th fr	29	2-year LRC 97.2% (ART) 82.2% (no-ART) $P = 0.04$ 2-year OS 89.8% (ART) 82.2% (No-ART) $P = 0.47$		Improvements in quality of life with ART
Chen et al[71]	51	266	LAHNC	60b 70μ	1	40 Gy (10-58Gy)	30	2-year LRC 88% (ART) 79% (No-ART) $P = 0.01$ 2-year OS 73% (ART) 79% (No-ART) $P = 0.55$	G III: 39% (ART) 30% (No-ART) $P = 0.45$	G III: 14% (ART) 19% (No-ART) $P = 0.71$
Zhao et al[72]	33	66	NPC	70	1	15th ($\pm$5) fr	38	3-year LRFS 72.7% (ART) 68.1% (No-ART) $P = 0.3$		No difference except less xerostomia and mucosal with ART for N2 and N3 patients

ART IN HEAD AND NECK CANCER

Table 2 Dosimetric Benefits of ART in Patients With Head and Neck Cancer (From Castelli et al)

Author (year)	Nb Patients	Replanning Strategies		Dosimetric Analysis			Dosimetric Benefit		
		Nb	Timing	Time Point to Cumulate the Dose	Method to Cumulate The Dose	Total Dose for the Comparison (Gy)	Parotid Gland (Dmean)	Spinal Cord (Dmax)	Target Volume (PTV)
Capelle (2012)[73]	20	1	3rd week	2	Average DVH	66	−0.6 Gy *	−0.6 Gy *	+0.5 Gy (D1%)*
Castelli (2015)[74]	15	6	Weekly	7	DIR	70	−3.8 Gy*	–	–
Dewan (2016)[75]	30	1	40 Gy	2	DVH	30	IL −6 Gy* CL −2.2 Gy	−66 Gy*	More uniform coverage Decrease V110% by 2*
Duma (2012)[76]	11	1	16th (9th-21st) fr	1	DVH	2	No variation	−0.14 Gy	–
Jensen (2012)[4]	15	2 to 4	– IL-3.8%	3 to 5	DIR	70	CL: − 11.5%†	–	Improvement of coverage by 8%
Olteanu (2014)[77]	10	2	8th and 18th fr	3	DIR	70	−6%†,*	–	Higher minimum and lower maximum doses
Schwartz (2013)[11]	22	1 or 2	16th and 22nd fr	2 or 3	DIR	70	−0.7Gy*	–	Increase coverage and dose homogeneity
Zhao (2011)[72]	33	1	15th (±) fr	2	DVH	37.5 Gy (20-50 Gy)	Decrease mean dose*	–	–

ART IN HEAD AND NECK CANCER

- Majority willing to increase the use of ART in head and neck
  - To improve clinical outcome
  - Improve productivity
  - Improve therapeutic ratio
- Barriers:
  - The lack of equipment
  - Lack of training
  - Lack of tools / support
  - Resource heavy
  - Time consuming

Krishnatry R et al, 2018

ART IN LUNG CANCER

- Chemoradiation to 60-70 Gy in locally advanced disease
- 6-7 week period
- The addition of immunotherapy increases survival
- No room for dose escalation
- 30-35% local recurrence
- Lung and heart toxicity effects survival

ART IN LUNG CANCER

Table 1 Lung Density Changes Observed Across Multiple Large Patient Studies During Radiation Therapy Treatments

Study	No. Patients	Tumor Anatomical Shift	Atelectasis	Pleural Effusion
Kwint (2014)	177	27%	19%	6%
Elsayad (2016)	71	10%	20%	25%
Moller (2014)	163	–	15%	8%
Van Zwienen (2008)	114	–	29%	13%

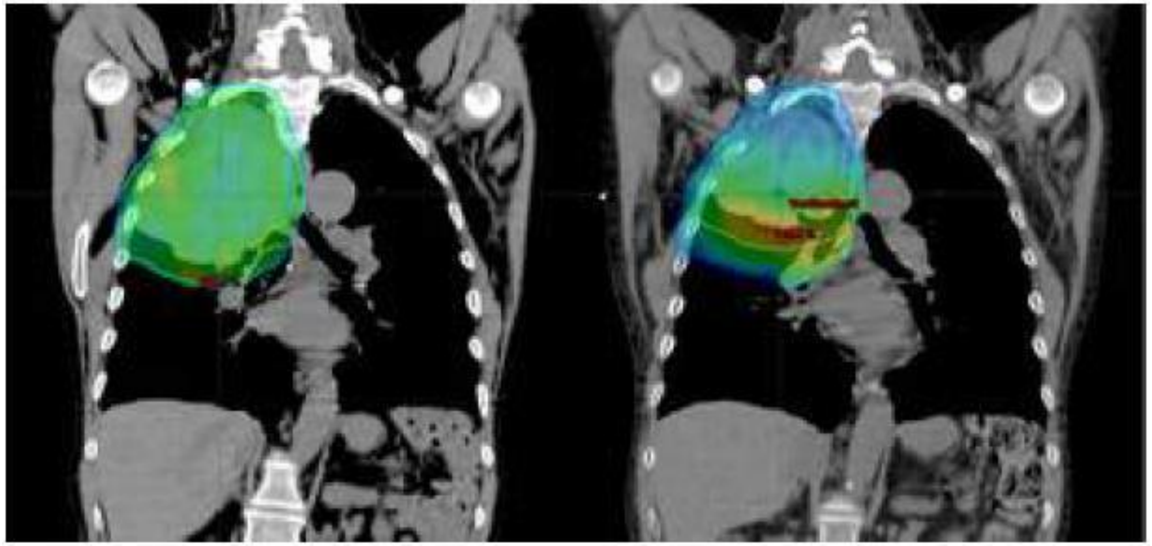
Table 2 Tumor Regression Rates for Patients Diagnosed With Stage III NSCLC Treated With Definitive Radiation

Study	No. Patients	Imaging Modality	Volume	Midtreatment Tumor Reduction		Near End of treatment Tumor Reduction	
				Median Fraction (Range)	Median Regression (Range)	Median Fraction (Range)	Median Regression (Range)
Kataria (2014)	15	Helical kVCT	GTVp	22nd-23rd	−34% (−13.8% to −73.0%)	–	–
Spoelstra (2009)	21	Helical kVCT	ITVp	15th (14th-17th)	Not reported (+47% to −25%)	–	–
Berkovic (2015)	41	kV CBCT	GTVp	–	–	30th	−42.1% (−4.0% to −69.3%)*
Fox (2009)	22	Helical kVCT	GTVp	15th (4th-20th)	−24.7% (+0.3% to −61.7%)	25th (21st-33rd)	−44.3% (−0.2% to −81.6%)
Wald (2017)	52	kV CBCT	GTVp	11th	−30% (+24.0% to −84.3%)	30th (24th-35th)	−62% (−3.4% to 91.2%)
Elsayad (2016)	37	kV CBCT	GTVp	–	–	30th	−35% (+22% to −78%)
Ramella (2017)	50	Helical kVCT	CTV	–	–	"When replanned"	−42% (−15% to −67%)*
Seibert (2007)	17	MVCT	GTVp	–	–	32nd (25th-37th)	−58.5% (+18% to −79%)

Studies Include a Combination of Sequential and Concurrent Chemotherapy.
* mean. CBCT, cone beam CT. GTVp, primary gross tumor volume. ITVp, primary internal target volume. CTV, clinical target volume.

ART IN LUNG CANCER

- 125 patient – 20% ART
- 3-4th week
- Daily CBCT
- Dose to PTV and OAR



ART IN LUNG CANCER

OAR	Constraints	$IMRT_{In}$	$IMRT_{Proj}$	$IMRT_{ADAPT}$	$IMRT_{In}$ vs. $IMRT_{Proj}$	$IMRT_{Proj}$ vs. $IMRT_{ADAPT}$
Lung	V_5 (cc)	50	54	40	0.01	0.003
	V_{20} (cc)	24	28	20	<0.001	<0.001
	D_{MLD} (cGy)	1429.45	1680.66	1167.59	<0.001	<0.001
Heart	V_{20} (%)	22.37	19.6	13.42	0.166	0.024
	V_{60} (%)	4.03	3.68	1.48	0.751	0.012
Spinal Cord	D_{MAX} (cGy)	4056.06	4527.32	3778.32	0.025	0.007
Esophagus	D_{MLD} (cGy)	2763.77	2994.32	2290.99	0.076	<0.001
	V_{40} (%)	35.12	38.07	27.24	0.146	0.006
	D_{MAX} (cGy)	6681052	6836.35	6815.68	0.009	0.927
Body	D_{MAX} (%)	110.57	114.5	109.76	<0.001	0.001

CLINICAL CHALLENGES FOR LUNG ART

Trial record **1 of 1** for: RTOG 1106/ACRIN 6697

Previous Study | Return to List | Next Study

Study of Positron Emission Tomography and Computed Tomography in Guiding Radiation Therapy in Patients With Stage III Non-small Cell Lung Cancer

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT01507428

Recruitment Status : Active, not recruiting
First Posted : January 10, 2012
Last Update Posted : January 22, 2020

– Which philosophy?

KEY TECHNOLOGIES FOR PRACTICAL WORKFLOW

- 3D imaging
- Assessment (manual evaluation to highly automated review of cumulative dose)
- Replanning (standard planning for offline – time!!!)
- QA

THE UNCERTAINTIES

- Deformable registration (DIR)
  - Commissioning
- Auto-segmentation
- Dose accumulation

HOW DO WE DO IT?

- Full neck radiotherapy, head and neck cancer
- Radixact® System
- 10/2018
- Ongoing adaptive workflow for linac treatments
- PreciseART® since mid 2019

PreciseART®
ACCURAY®

HOW DO WE DO IT?

- All patients are potential for adaptation
- Enroll to PreciseART® during plan approval
- Template (OAR and PTV)
- Dedicated IGRT dosimetrist from the second week
  - 2 days a week
- PreciseART® software check

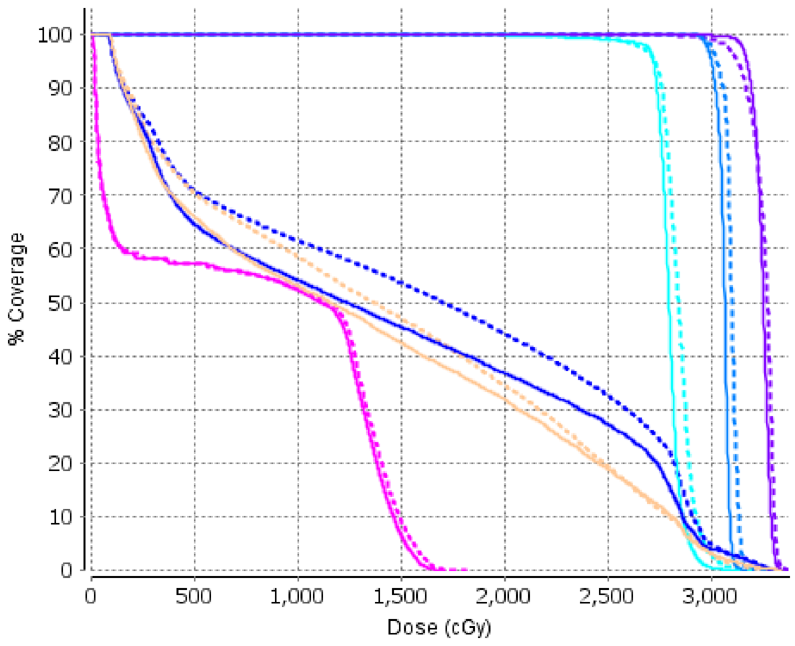
PreciseART®
ACCURAY®

HOW DO WE

Expected Dose vs Accumulated Dose

Contour	Constraint Name	Expected Planned	Fulfilled	Accumulated Dose	Fulfilled	% Change
PTV60rev	PTV60rev, D95%>60Gy	2922.32 cGy	✓	2730.12 cGy	✗	0.29
PTV66rev	PTV66rev, D95%>66Gy	3002.89 cGy	✓	3029.26 cGy	✓	0.88
PTV70rev	PTV70rev, D95%>70Gy	3273.76 cGy	✓	3130.19 cGy	✗	-1.37
L Parotid	L Parotid, Dmean<30 Gy	1319.89 cGy	✓	1711.74 cGy	✗	29.68
Oral Cavity	Oral Cavity Dmean<30Gy	1632.58 cGy	✓	1707.11 cGy	✓	4.57
PTV60rev	PTV60rev, Dmax<66Gy	3134.31 cGy	✓	3227.4 cGy	✓	2.97
PTV66rev	PTV66rev, Dmax<69.5 Gy	3168.73 cGy	✓	3268.54 cGy	✓	3.15
PTV70rev	PTV70rev, Dmax<77Gy	3343.44 cGy	✓	3374 cGy	✓	0.91
R Parotid	R Parotid, Dmean<30Gy	1414.99 cGy	✓	1799.2 cGy	✗	27.15
Spinal Cord	Spinal Cord, Dmax<50 Gy	1711.13 cGy	✓	1821.12 cGy	✓	6.43

Expected Planned Dose vs Accumulated Dose



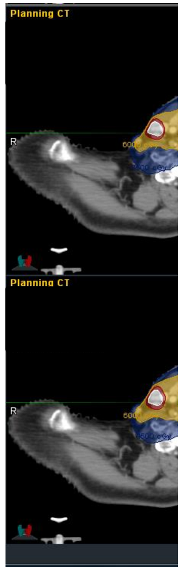
Dose ID	Line Style	Dose Details
D1	—	Expected Planned Dose
D2	- - -	Accumulated Dose

Contour	Color	Max Dose		Min Dose		Mean Dose	
		D1	D2	D1	D2	D1	D2
L Parotid		3,335.02	3,333.02	91.67	87.11	1,319.89	1,711.74
PTV60rev		3,134.31	3,227.40	1,622.94	1,724.53	2,795.79	2,840.00
PTV66rev		3,168.73	3,268.54	2,897.60	2,900.96	3,061.15	3,097.63
PTV70rev		3,343.44	3,374.00	2,830.03	2,487.12	3,247.73	3,253.09
R Parotid		3,286.81	3,297.80	86.62	82.27	1,414.99	1,799.20
Spinal Cord		1,711.13	1,821.12	13.05	10.35	770.26	782.97

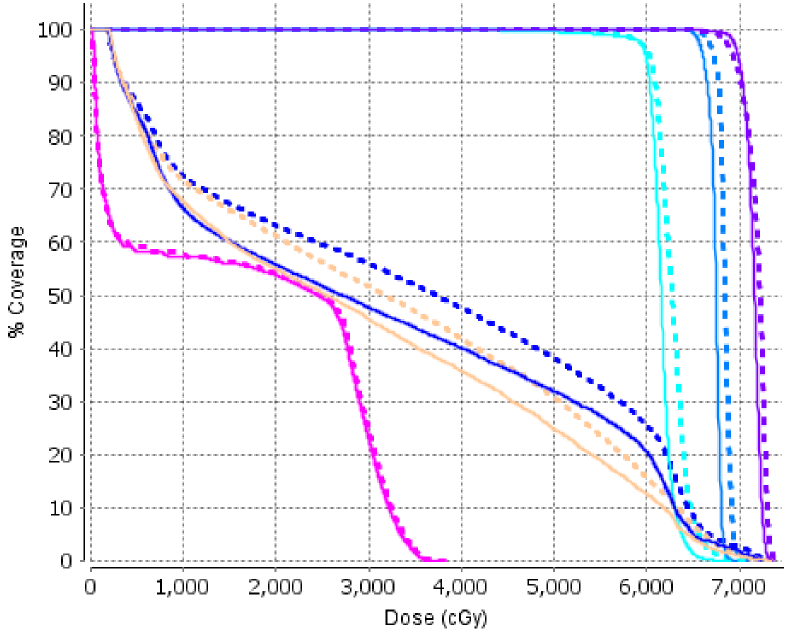
HOW DO WE

Total Planned vs Projected Dose

Contour	Constraint Name	Total Planned	Fulfilled	Projected Dose	Fulfilled	% Change
Oral Cavity	Oral Cavity Dmean<30Gy	2991.67 cGy	✓	3131.11 cGy	✗	4.66
PTV60rev	PTV60rev, D95%>60Gy	6029.11 cGy	✓	6031.68 cGy	✓	0.02
PTV60rev	PTV60rev, Dmax<66Gy	6595.48 cGy	✓	7148.27 cGy	✗	8.38
PTV66rev	PTV66rev, Dmax<69.5 Gy	6941.2 cGy	✓	7201.51 cGy	✗	3.75
PTV70rev	PTV70rev, D95%>70Gy	7182.26 cGy	✓	6932.33 cGy	✗	-0.72
R Parotid	R Parotid, Dmean<30Gy	2912.98 cGy	✓	3526.5 cGy	✗	21.06
L Parotid	L Parotid, Dmean<30 Gy	2903.75 cGy	✓	3226.55 cGy	✗	11.12
PTV66rev	PTV66rev, D95%>66Gy	6606.35 cGy	✓	6721.32 cGy	✓	1.74
PTV70rev	PTV70rev, Dmax<77Gy	7355.56 cGy	✓	7455.9 cGy	✓	1.36
Spinal Cord	Spinal Cord, Dmax<50 Gy	3764.5 cGy	✓	3866.41 cGy	✓	2.71

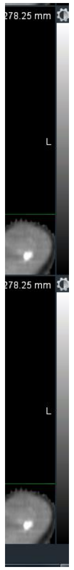


Total Planned Dose vs Projected Dose



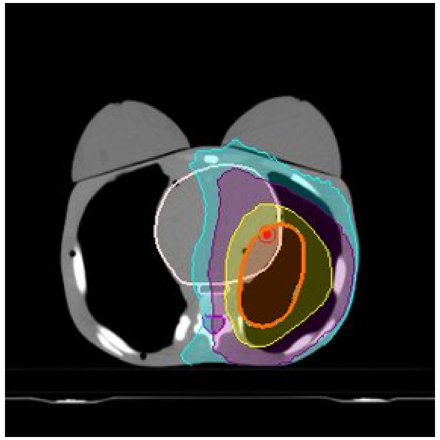
Dose ID	Line Style	Dose Details
D1	——	Total Planned Dose
D2	▪ ▪	Projected Dose

Contour	Color	Max Dose		Min Dose		Mean Dose	
		D1	D2	D1	D2	D1	D2
L Parotid		7,337.04	7,347.82	201.68	188.18	2,903.75	3,226.55
PTV60rev		6,895.48	7,148.27	3,570.46	3,921.93	6,150.73	6,271.64
PTV66rev		6,971.20	7,201.51	6,374.72	6,397.37	6,734.53	6,837.93
PTV70rev		7,355.56	7,455.90	6,226.07	6,104.52	7,145.02	7,183.52
R Parotid		7,230.99	7,290.71	190.56	179.53	2,912.98	3,526.50
Spinal Cord		3,764.50	3,866.41	28.71	22.36	1,694.57	1,716.70

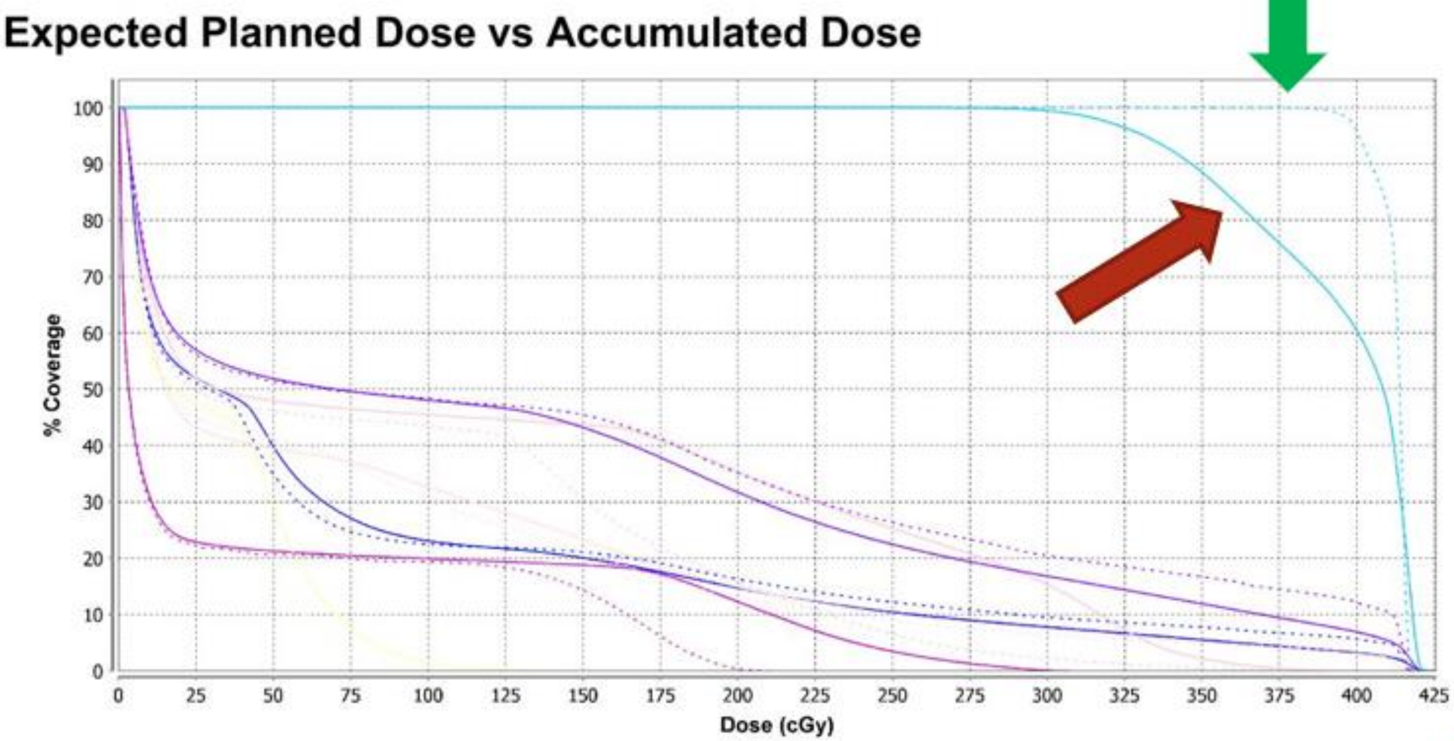


HOW DO WE DO IT?

PLAN
VOLÜMLER



PLAN CT



SUMMARY…

- Adaptive is in the frame
- More technological evolution
- Workload – time
- Selected patients
- Data!!!