Radiation in Locally Advanced Non-Small Cell Lung Cancer

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Flow of my Talk

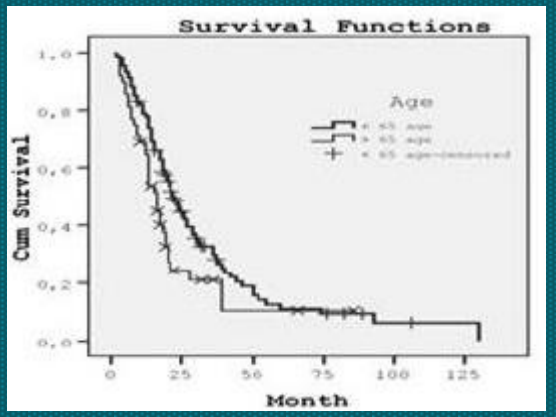
- Selection of patients
- Time, dose and fractionations
- Radiation Volumes
- OAR Constraints
- Outcome and complications

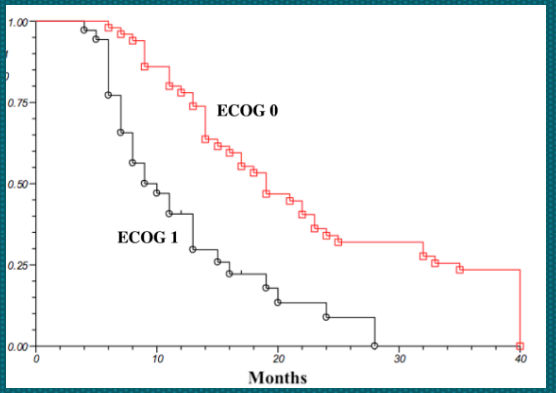
What is Locally Advanced Lung Cancer

	N0	N1	N2	N3
T1	IA	IIB	IIIA	IIIB
T2a	IB	IIB	IIIA	IIIB
T2b	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIB	IIIC
T4	IIIA	IIIA	IIIB	IIIC
M1a	IVA	IVA	IVA	IVA
M1b	IVA	IVA	IVA	IVA
M1c	IVB	IVB	IVB	IVB

Patient factors

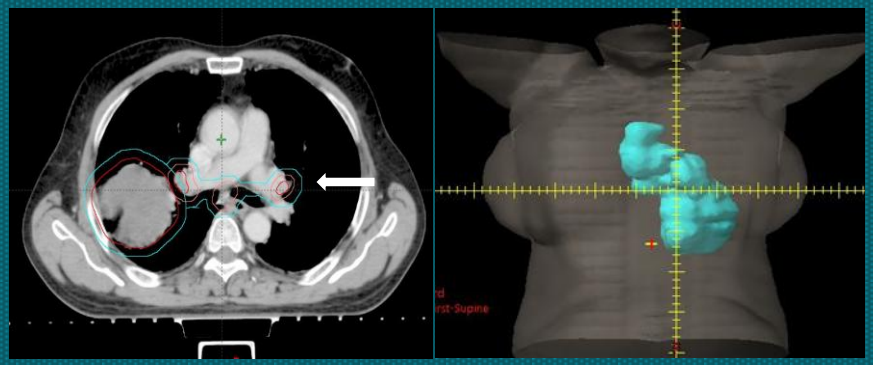
- Age - No cut-off
- Performance status (KPS/ECOG) – 70-100/0-2
- Comorbidities – COPD, DM, HT
- PFT parameters – FEV1>50% predicted or ≥1.0 L and DLCO >40%
- Interstitial lung disease





Tumor factors

- T stage - T1-T4 (except nodules in different lobe)
- Nodal Status
- Size/PTV Volume - > 700cc –bad prognosis
- Location and Laterality
- Collapse: Major airway involved



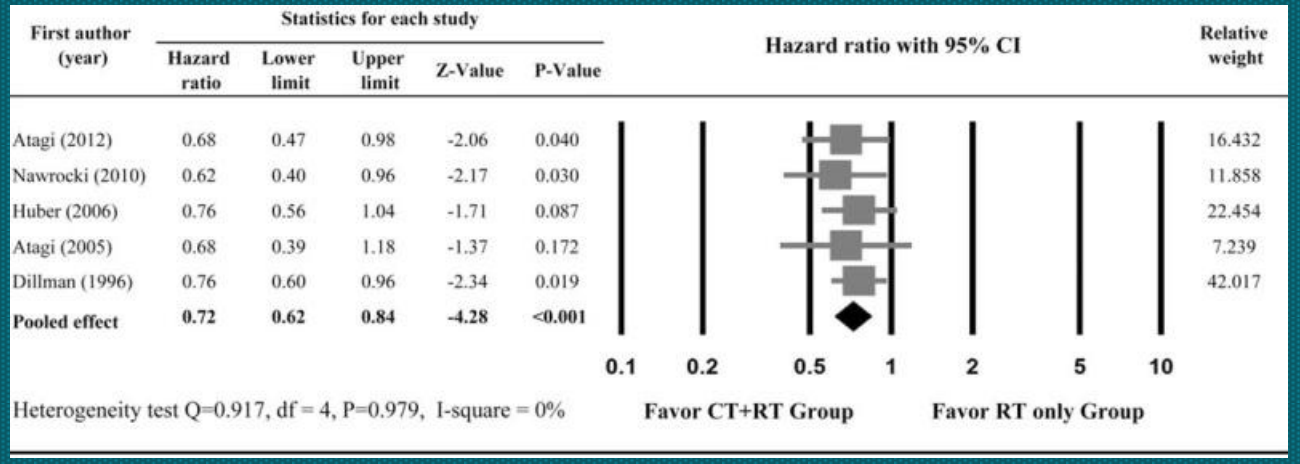
Treatment factors

- Motion management – Very essential
- Linear accelerator
- Planning System – tissue heterogeneity corrections
- Pulmonary rehabilitation

Radiation Alone or Combined with Chemo

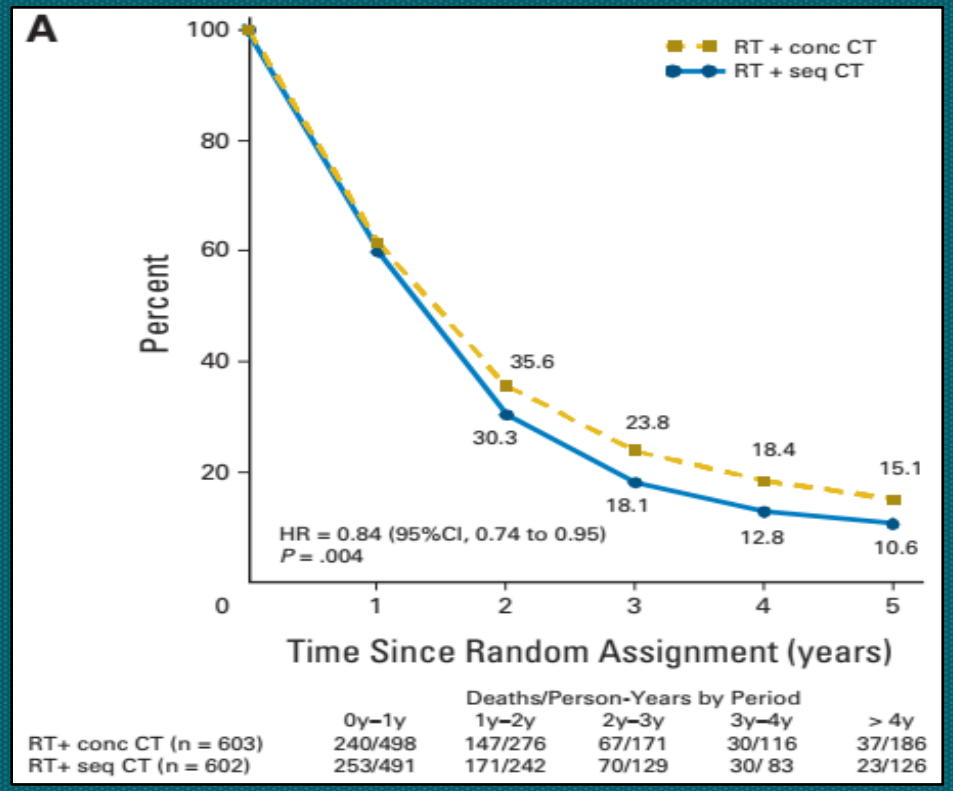
Two Year Overall Survival

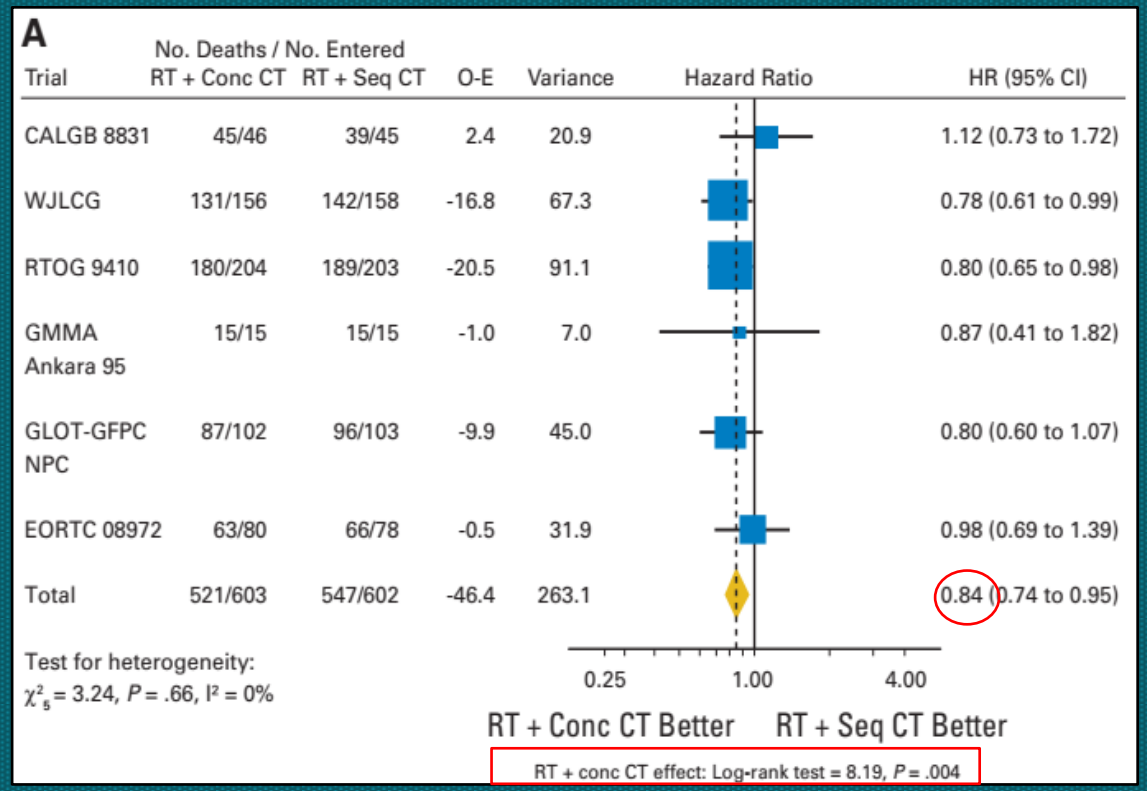
Trial	Pts	RT	CT--->RT
Finnish	238	17%	19%
NCCTG	107	16%	21%
CALGB	155	13%	26%
IGR-French	331	14%	21%



Hung et al. Medicine (2019) 98:27

Timing of Radiation

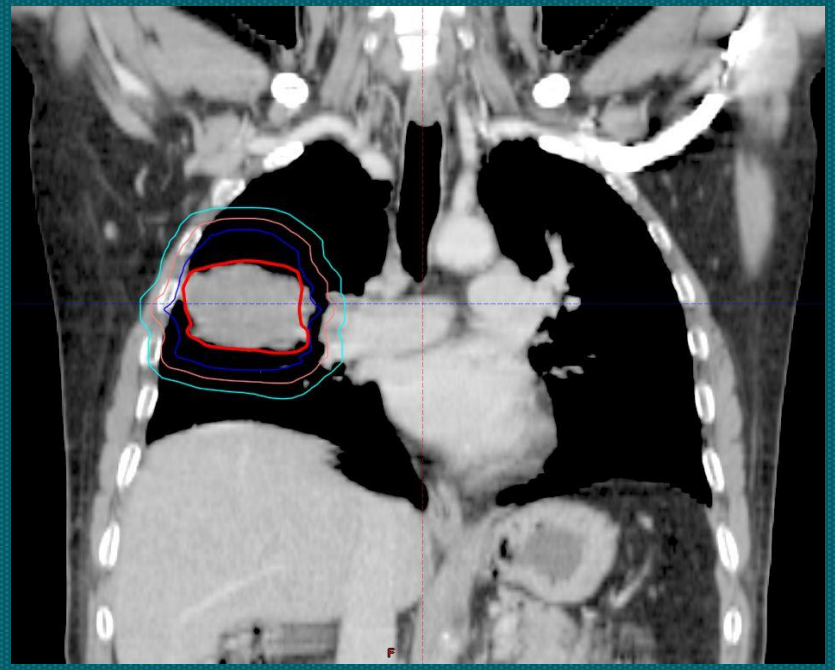


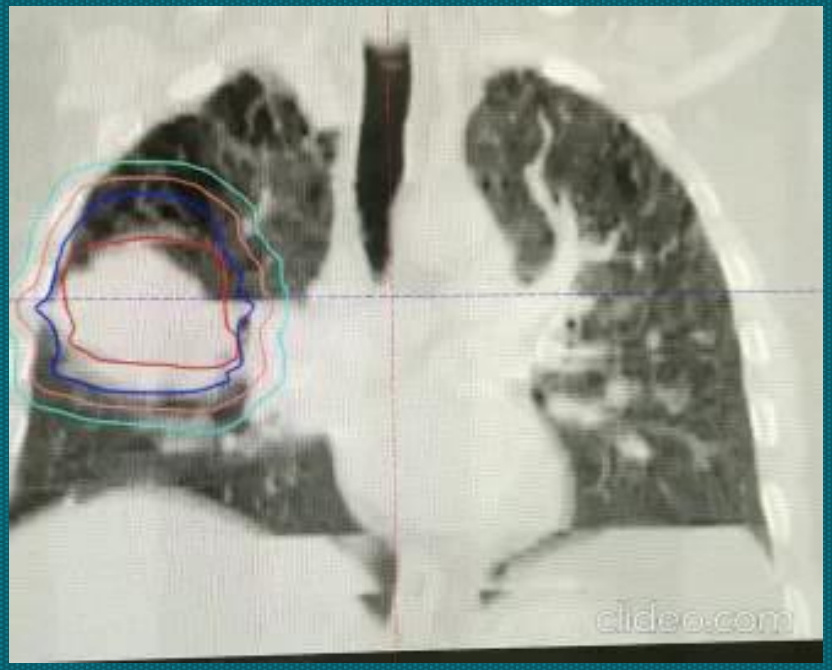


Absolute benefit of 5.7% (from 18.1% to 23.8%) at 3 years and 4.5% at 5 years

Auperin A et al. J Clin Oncol. 2010

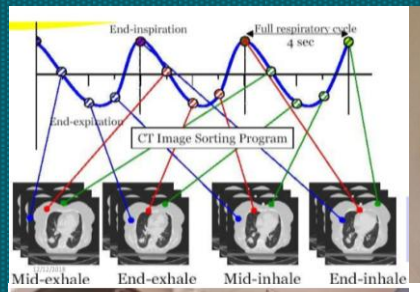
Motion Management

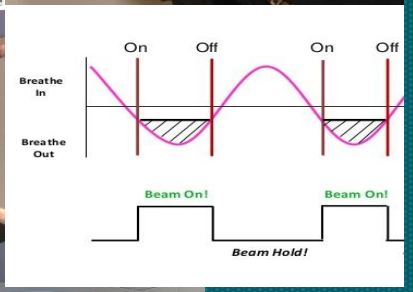




Methods to Account Tumor Motion

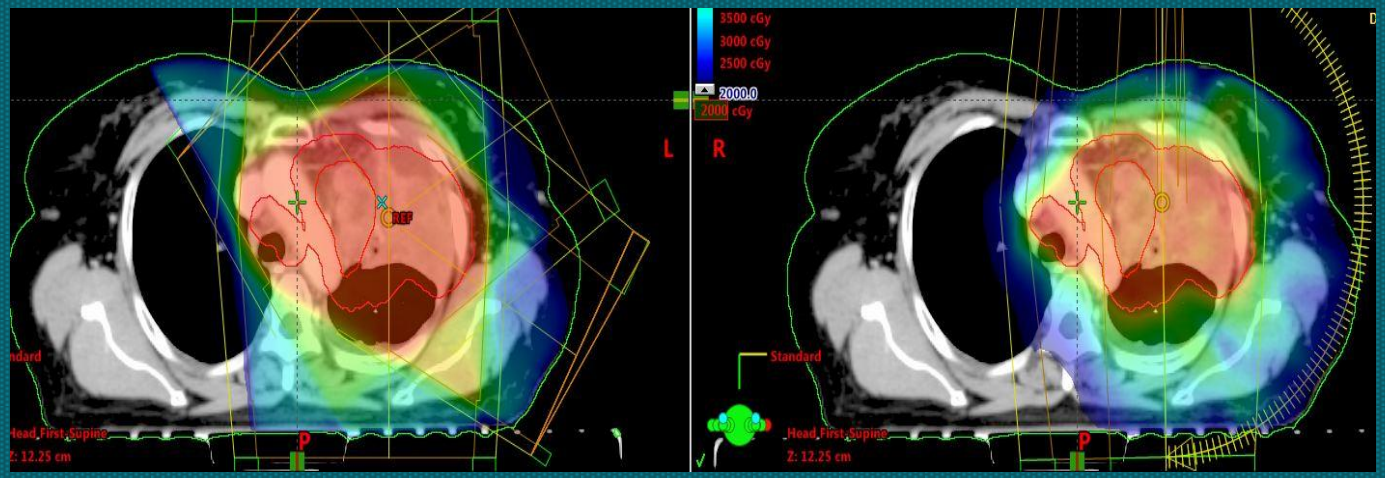
- Motion encompassing
- Forced shallow breathing
- Breath Hold
- Respiratory Gating
- Respiration Tracking





Radiation Techniques

- IMRT is more conformal and reduces normal tissue doses better than 3D CRT
- In RTOG 0617 – inspite of larger volumes and more IIIB disease, IMRT reduces the risk of pneumonitis
- No difference in overall survival

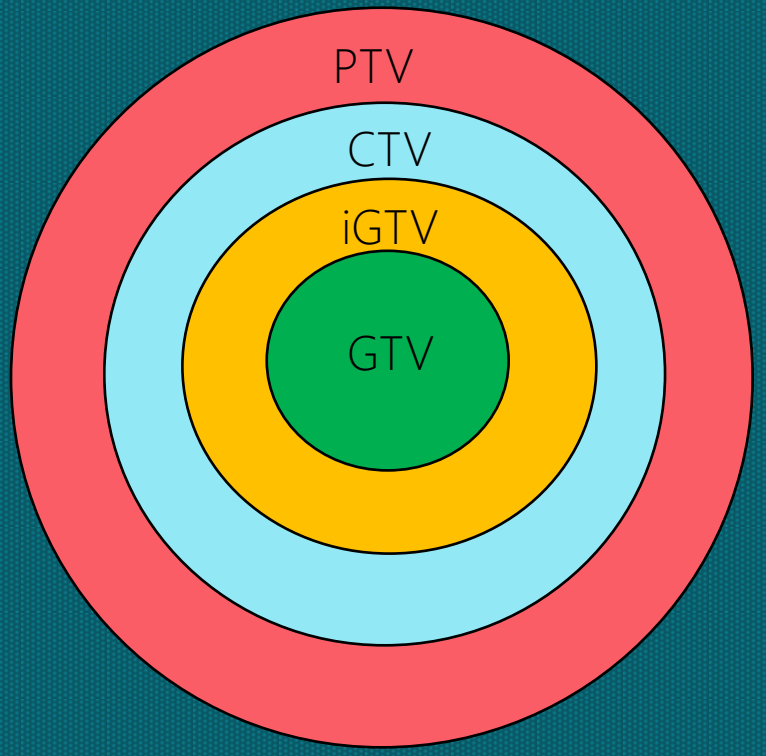


3D-CRT IMRT

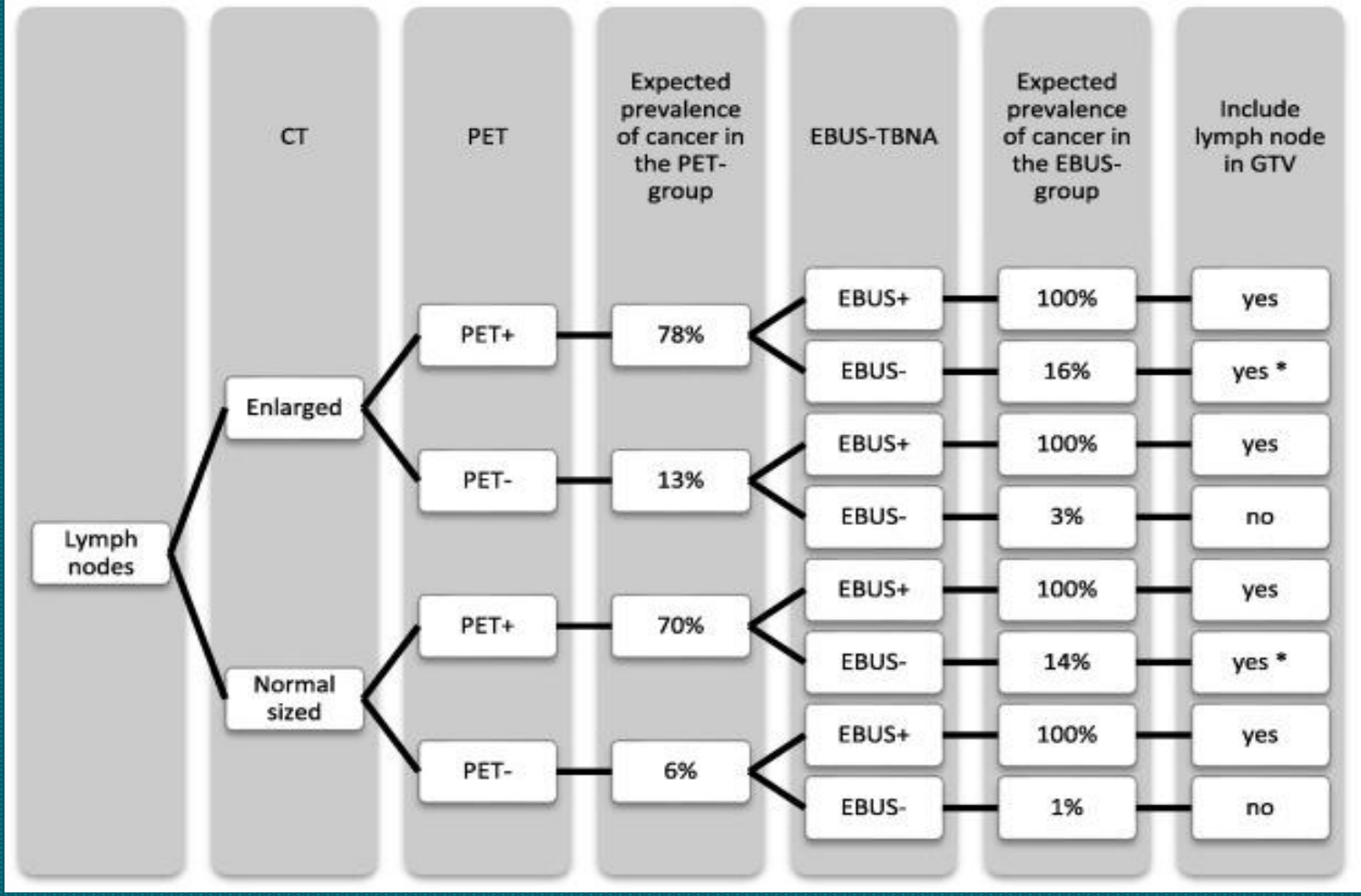
Outcome	3D-CRT	IMRT,	P value
2-year OS	49.4	53.2	0.597
2-year PFS	27.0	25.2	0.595
Pneumonitis	7.9%	3.5%	0.03
Heart V40 (%)	11.4	6.8	0.003

Radiation Volumes

- GTV – Primary + Nodes (>1cm or SUV>3)
- No ENI
- ITV (iGTV) – GTV + Resp motion
- CTV – ITV + 0.7 cm
- PTV – CTV + 0.5 cm
- Prescription – Planning target volume

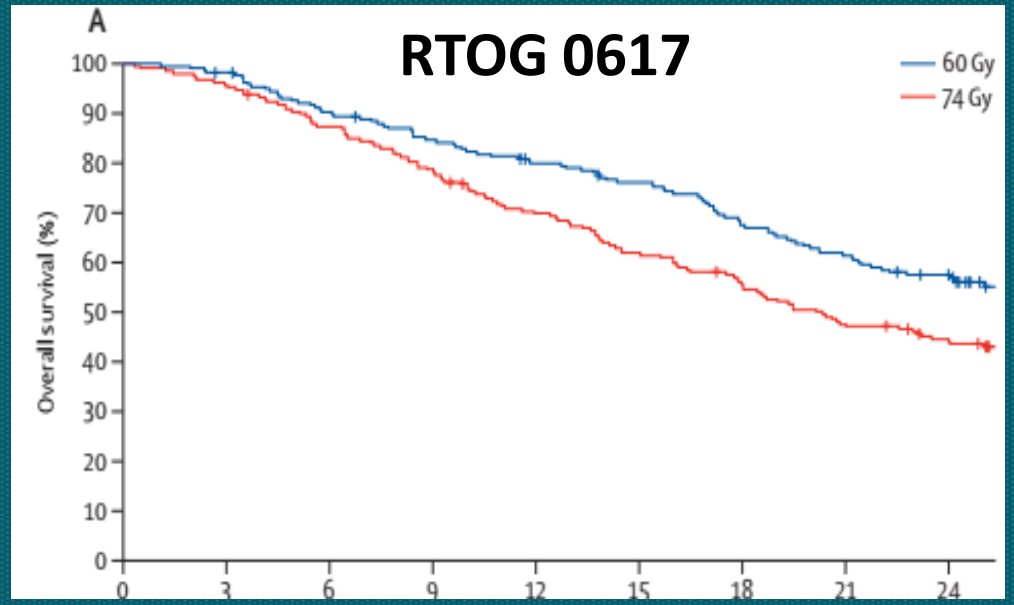


Radiation Volumes - Nodal



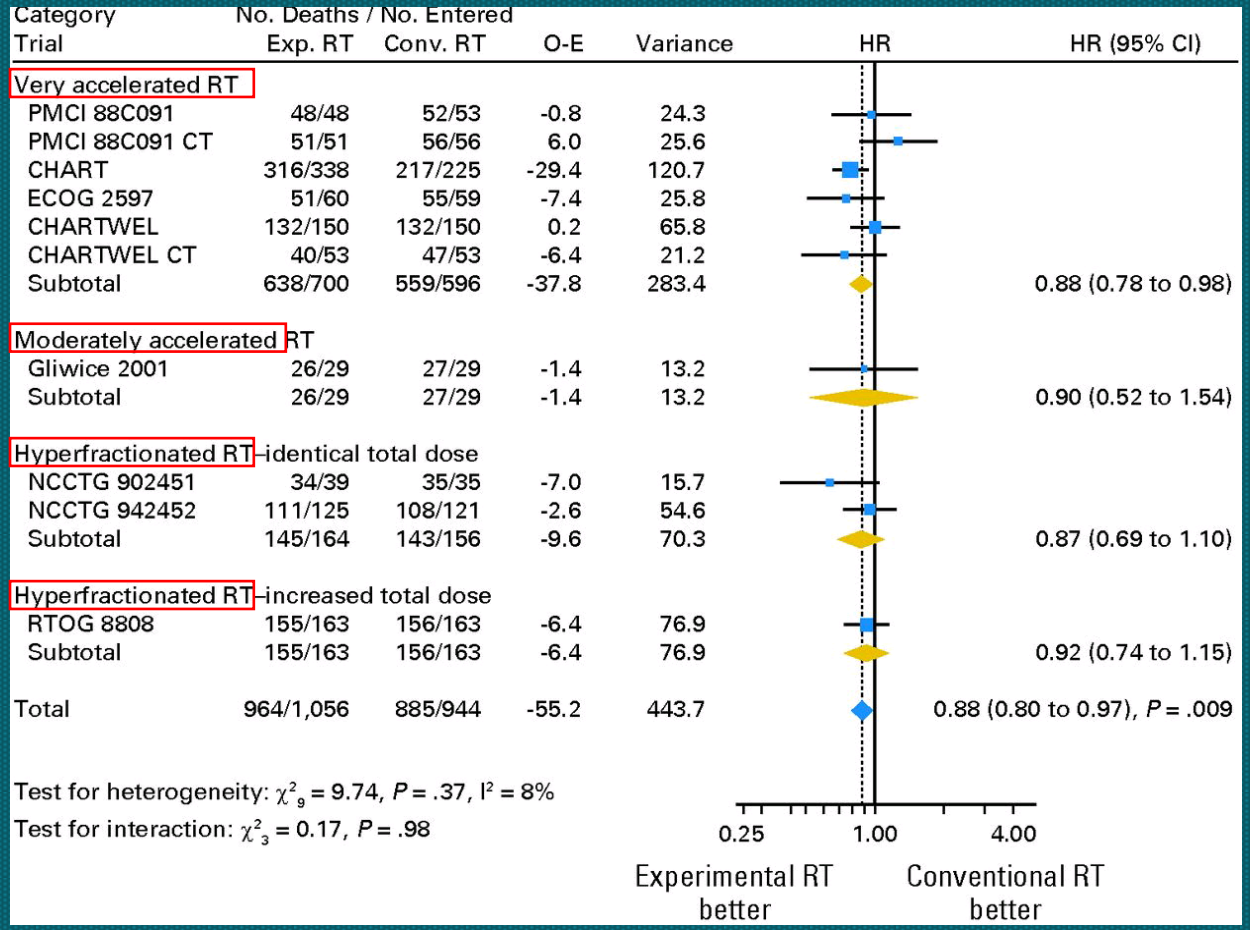
Dose and fractionation

- Standard - 60-66 in 30-33 fractions
- No proven role of uniform dose escalation
- Hypofractionation – could increase risk of RIP



Outcome	60 Gy	74 Gy	P value
Med OS	28.7	20.3	0.007
5 yr OS	32.1%	23%	0.004
5 yr PFS	18.3%	13%	0.055

Accelerated fractionation schedules



- 5-yr absolute benefit in OS of 2.5%
- Esophagitis rate significantly higher with hyper fractionation

Mauguen A et al. J Clin Oncol 2012

Organ at Risk Constraints

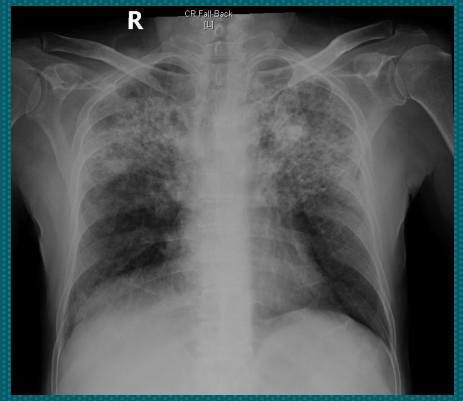
Organs at Risk	Dose Metrics	Acceptable level
Lung	V20	<30-35%
	MLD	<20Gy
Spinal Cord	Dmax	<45Gy
SC PRV (5mm)	Dmax	<50Gy
Heart	Mean	<30 Gy
	V40	<30Gy
Oesophagus	Dmax	≤63 Gy
	Mean	≤34 Gy

Outcome of CTRT

Trial (CTRT Arm)	Median OS (months)	3 year OS
INT 0139 (2009)	22.2	30% (appx)
RTOG 0617 (2015)	28.7	32% (5yr)
Proclaim (2016)	25	37%
PACIFIC (2017)	29.1	43.5%

Complications of CRT

- Radiation Pneumonitis – ≥ Gr 3 - 15-20 %
- Oesophagitis – length of oesophagus and Etoposide
- Radiation Induced Heart Disease – RTOG 0617 attributed poorer OS



Factors impacting RIP

Age > 65 yrs
Lung Doses (MLD>20Gy, V20>35%)
PFT
Smoking
Taxanes CT

Treatment - Short course steroids

CTCAE Scale

PFT	Cutoff point	No Pneumonitis	Pneumonitis	HR	95% CI	*P* value
FEV1	<1.9	2 (9.1%)	7 (46.7%)	3.21	0.93–11.16	**0.017**
	≥1.9	20 (90.9%)	8 (53.3%)			
FeNO	<17.5	13 (59.1%)	3 (20%)	1.90	1.10–3.28	**0.041**
	≥17.5	9 (40.9%)	12 (80%)			
DLCO	<18.9	7 (31.2%)	12 (80%)	2.26	1.21–4.22	**0.007**
	≥18.9	15 (68.2%)	3 (20%)			

Bouscoulet et al. Respiratory Research (2018) 19:72

Predictors of Pneumonitis

- Lung –PTV V20Gy – significantly correlated with incidence of pneumonitis
- Mean Lung dose <20 Gy

Table 6. Correlation between V_{20} and severity of pneumonitis

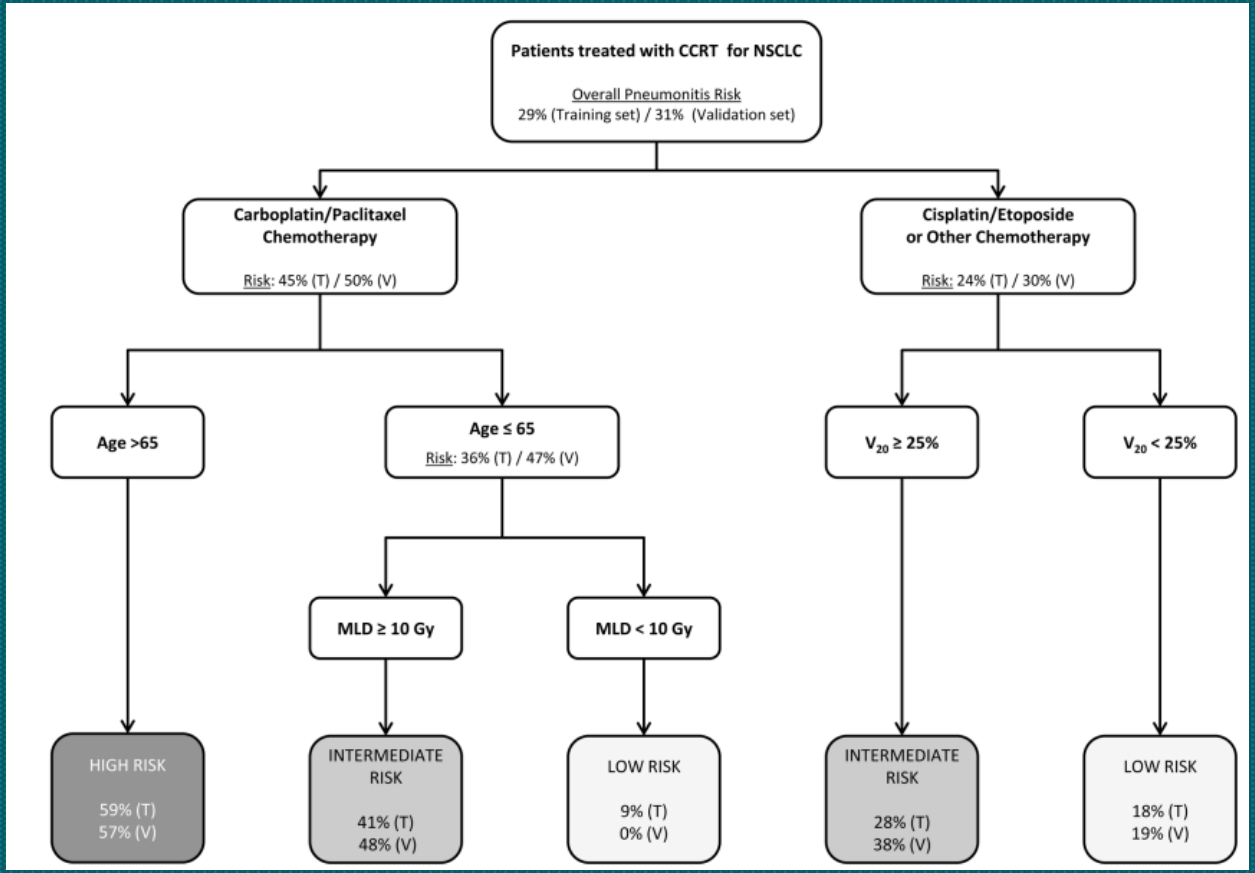
V_{20} (%)	Grade 2 (%)	Grade 3–5 (%)
<22	0	0
22–31	8	8
32–40	13	5 (1 fatal)
>40	19	23 (3 fatal)

Gaspar et al 2006	V20 ≤35%	V20 >35%
RP≥ Gr 3	4 %	10 %
Median survival	24 months	12 months

Graham et al; IJROBP, 1999

CLINICAL INVESTIGATION | VOLUME 85, ISSUE 2, P444-450, FEBRUARY 01, 2013

Predicting Radiation Pneumonitis After Chemoradiation Therapy for Lung Cancer: An International Individual Patient Data Meta-analysis

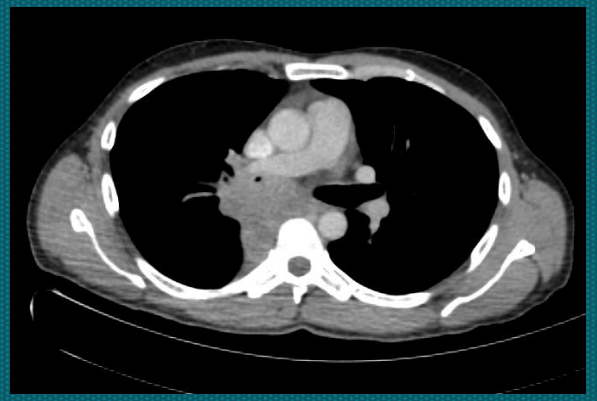


V20 Gy	Symptomatic pneumonitis (≥ Gr 2)	Fatal Pneumonitis
<20%	18.4%	0.0%
20-29.99%	30.3%	1.0%
30-39.99%	32.6%	2.9%
≥ 40%	35.9%	3.5%

Palma et al; IJROBP: 2014

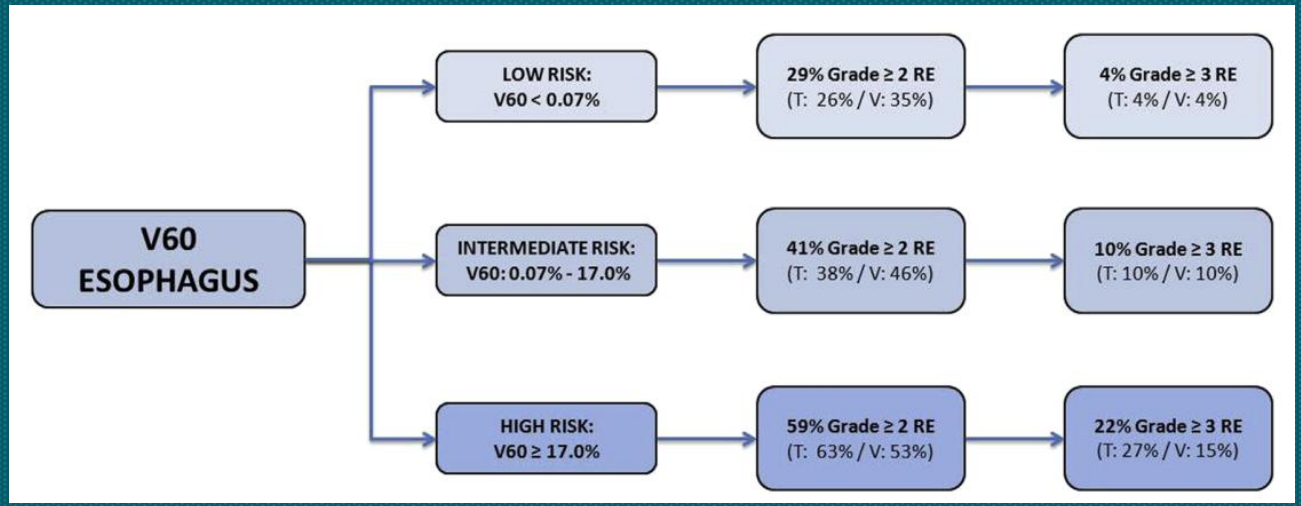
Predictors of Esophagitis

- Usually starts from 4 - 5th week
- Mean dose> 34 Gy
- Etoposide
- V60
- SUVpeak



CLINICAL INVESTIGATION | VOLUME 87, ISSUE 4, P690-696, NOVEMBER 15, 2013

Predicting Esophagitis After Chemoradiation Therapy for Non-Small Cell Lung Cancer: An Individual Patient Data Meta-Analysis



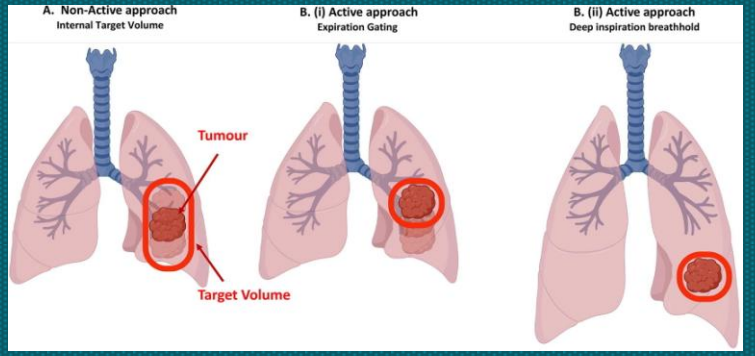
Palma et al; IJROBP: 2013

Cardiac Toxicity

RTOG 0617

Appendix 6
RT Endpoint: Multivariate Cox Model of Overall Survival
(n=407)

Covariate	Comparison	Dead/Total RL	Dead/Total Group 2	HR (95% CI)	p-value*
Radiation Level	Standard Dose (RL) vs. High Dose	121/208	136/199	1.34 (1.04, 1.73)	0.0213
Maximum related esophagitis/dysphagia grade	Maximum grade < 3 (RL) vs. Maximum grade ≥ 3	210/349	47/58	1.54 (1.11, 2.15)	0.0102
Volume of PTV	Continuous	257/407		1.000 (1.000, 1.001)	0.0729
Heart V5	Continuous	257/407		1.007 (1.002, 1.011)	0.0035
Zubrod PS	0 (RL) vs. 1	151/240	106/167	1.14 (0.89, 1.47)	0.3045
PET Staging	No (RL) vs. Yes	30/39	227/368	0.77 (0.52, 1.13)	0.1766
Gender	Male (RL) vs. Female	153/240	104/167	0.97 (0.74, 1.26)	0.7975
Histology	Non-squamous (RL) vs. Squamous	146/228	111/179	1.01 (0.78, 1.31)	0.9380



Dose Volume Constraints	Study
Referred reader to trial protocols/guidelines	
RTOG 0618 and RTOG 0236	Troost et al, 2020
RTOG 0617 for NSCLC, RTOG 0538 for SCLC	Vinogradskiy et al, 2018
Dose Volume Constraint Specified	
MHD < 26 Gy	Kapoor et al, 2020
MHD < 26 Gy, Dmax: V25 Gy < 10%, V30 Gy < 46%, V50 Gy < 40%	Creemers et al, 2019
MHD ≤ 26 Gy, V30Gy ≤ 40%, V40Gy ≤ 30%	Shao et al, 2019
MHD < 32 Gy	Li et al, 2020
MHD < 35 Gy	Kenamond et al, 2018
MHD ≤ 30 Gy	Wu et al, 2018
MHD < 35 Gy	Thomas et al, 2018
MHD < 46 Gy, V50 < 20%	Ottosson et al, 2015
MHD < 26 Gy, V30 < 40 Gy	Zhang et al, 2017
MHD < 15 Gy	Gala et al, 2017
Max dose ≤ 35 Gy, V40Gy ≤ 60%	Xu et al, 2017
D1cc < 78 Gy	Hoffmann et al, 2017
V20Gy < 20%	Bansal et al, 2019
V25Gy < 50%, V40Gy ≤ 30%	Josipovic et al, 2018
V30Gy ≤ 50%	Jaksic et al, 2018
V30Gy ≤ 50%, V45Gy ≤ 35%	Jeter et al, 2018
V40Gy ≤ 30%	Wong et al, 2020
V40Gy < 66%, V50Gy < 66%,V66Gy < 33%	van-Diessen et al, 2019
V45Gy < 66%	Waxweiler et al, 2017
V45Gy < 67%, V65Gy < 33%	Zhao et al, 2020
V60Gy < 33%	Temelli et al, 2020

Kearney et al; Radiother Oncol:2022

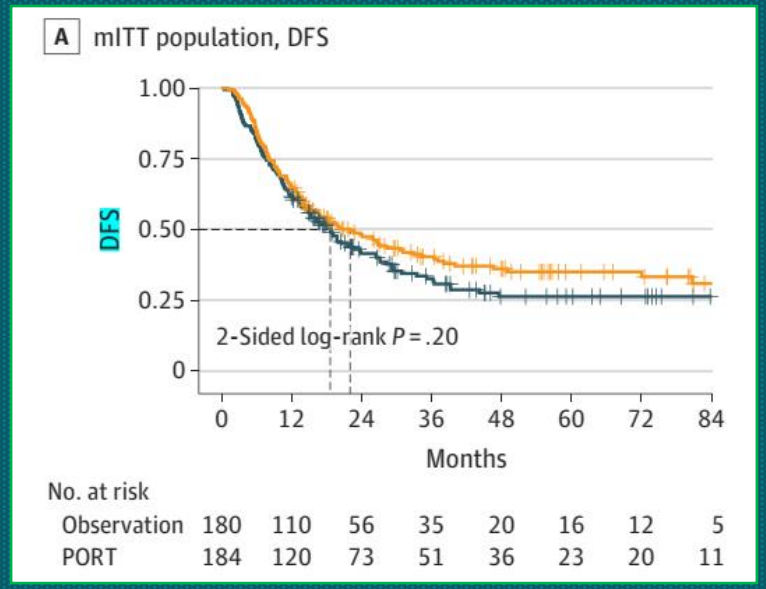
JAMA Oncology | Original Investigation

Effect of Postoperative Radiotherapy for Patients With pIIIA-N2 Non–Small Cell Lung Cancer After Complete Resection and Adjuvant Chemotherapy

The Phase 3 PORT-C Randomized Clinical Trial

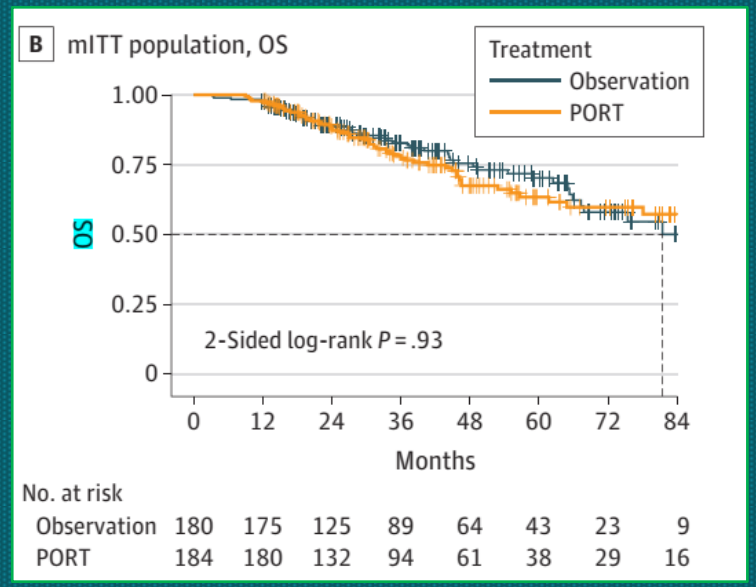
Median FU – 46 months

Median – 22.1 vs 18.6 months
3-year – 40.5% vs 32.7%



Disease free survival

Median – NR vs 81.5 months
3-year – 78.3% vs 82.8%



Overall survival

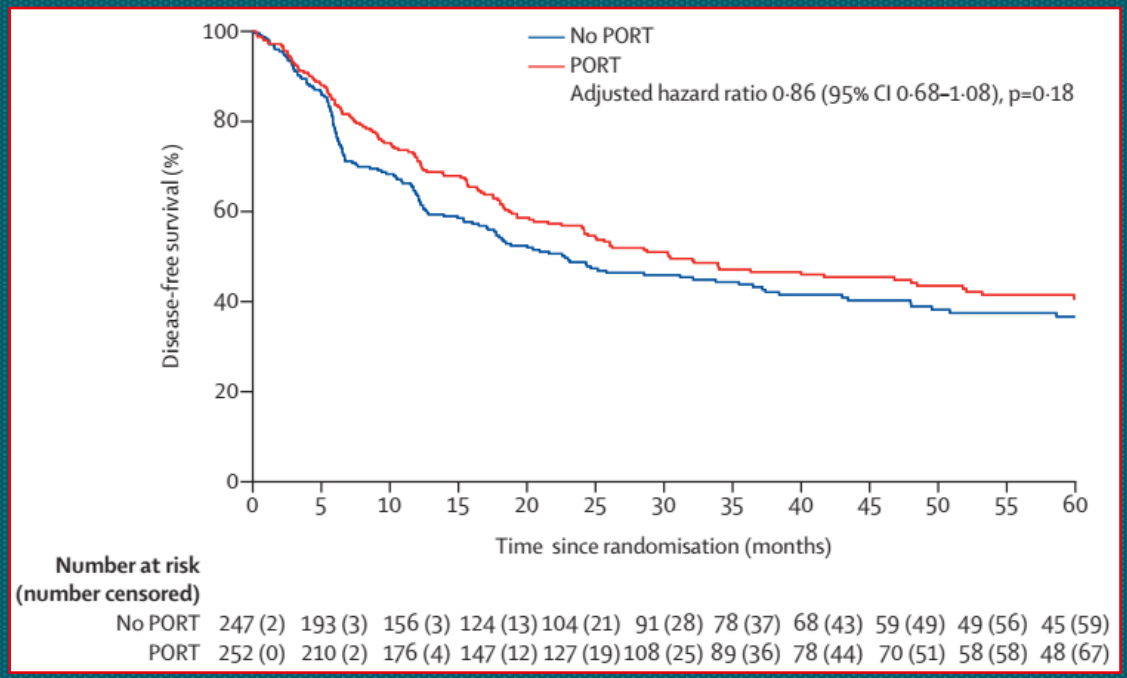
Hui et al; JAMA Oncol; 2021

Postoperative radiotherapy versus no postoperative radiotherapy in patients with completely resected non-small-cell lung cancer and proven mediastinal N2 involvement (Lung ART): an open-label, randomised, phase 3 trial

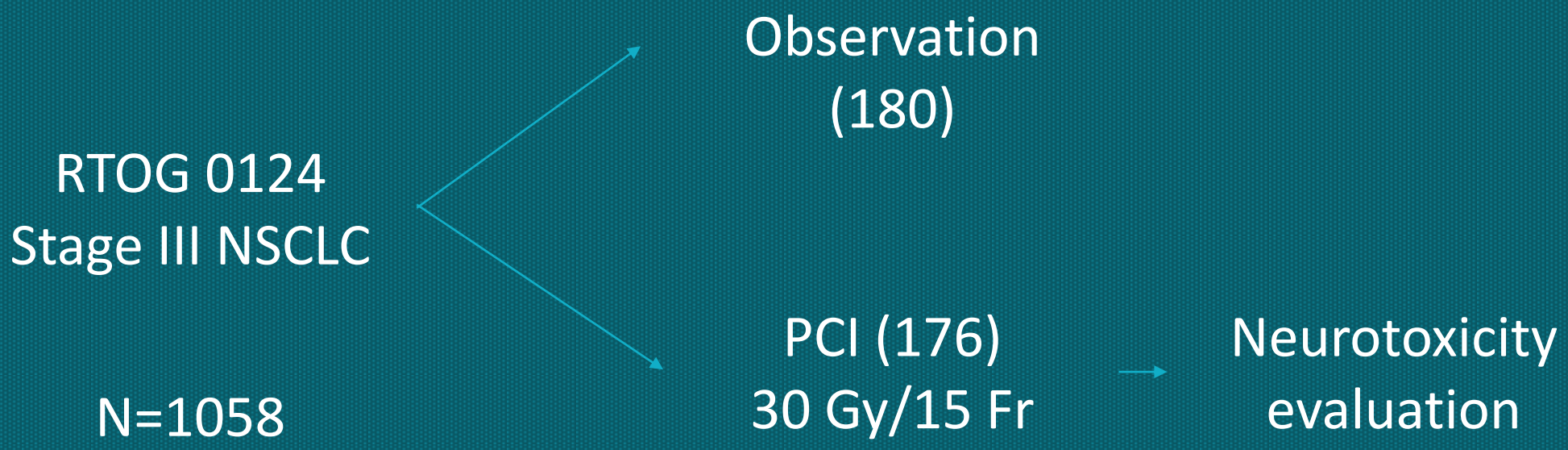
Cecile Le Pechoux,

Lancet Oncol 2022; 23: 104–14

Total received dose (in Gy)†		
≤50	7/241 (3%)	..
51–57	231/241 (96%)	..
>57	3 (1%)	..
Main radiotherapy variables†		
Lung V20	23% (17–27)	..
Mean lung dose (Gy)	13 (10–15)	..
Mean heart dose (Gy)	13 (8–19)	..
Heart V35	15% (8–24)	..
PORT technique†		
Three-dimensional conformal radiotherapy	201/226 (89%)	..
Intensity-modulated radiotherapy	25/226 (11%)	..
Missing information	15	..



Prophylactic Cranial Irradiation



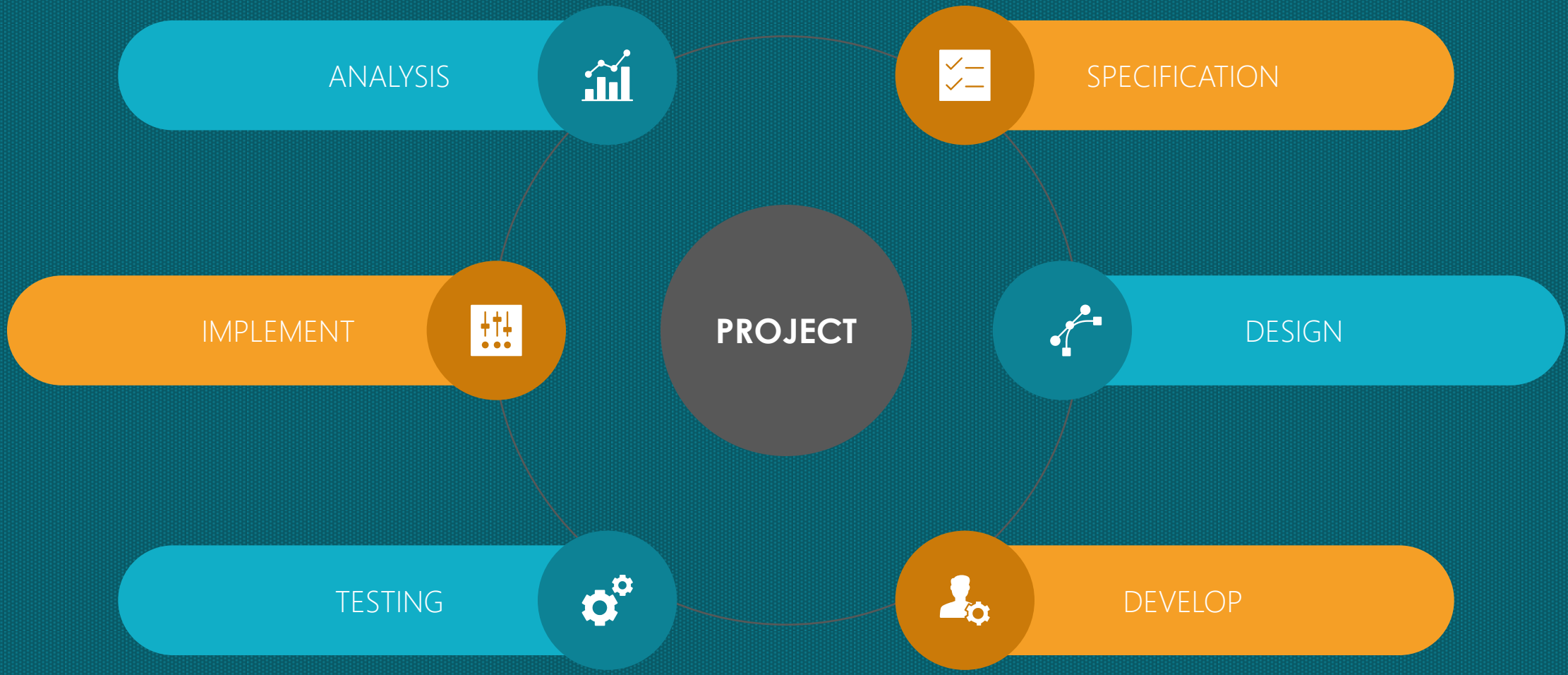
10 year OS was 13.3% Vs 17% (p-NS) and DFS were not significantly different

10 year rates of BM were significantly different (28.3 vs 16.7% for observation and PCI *P*.003)

Sun et al; JAMA Oncol: 2019

THANK YOU

Project Analysis



Project Analysis

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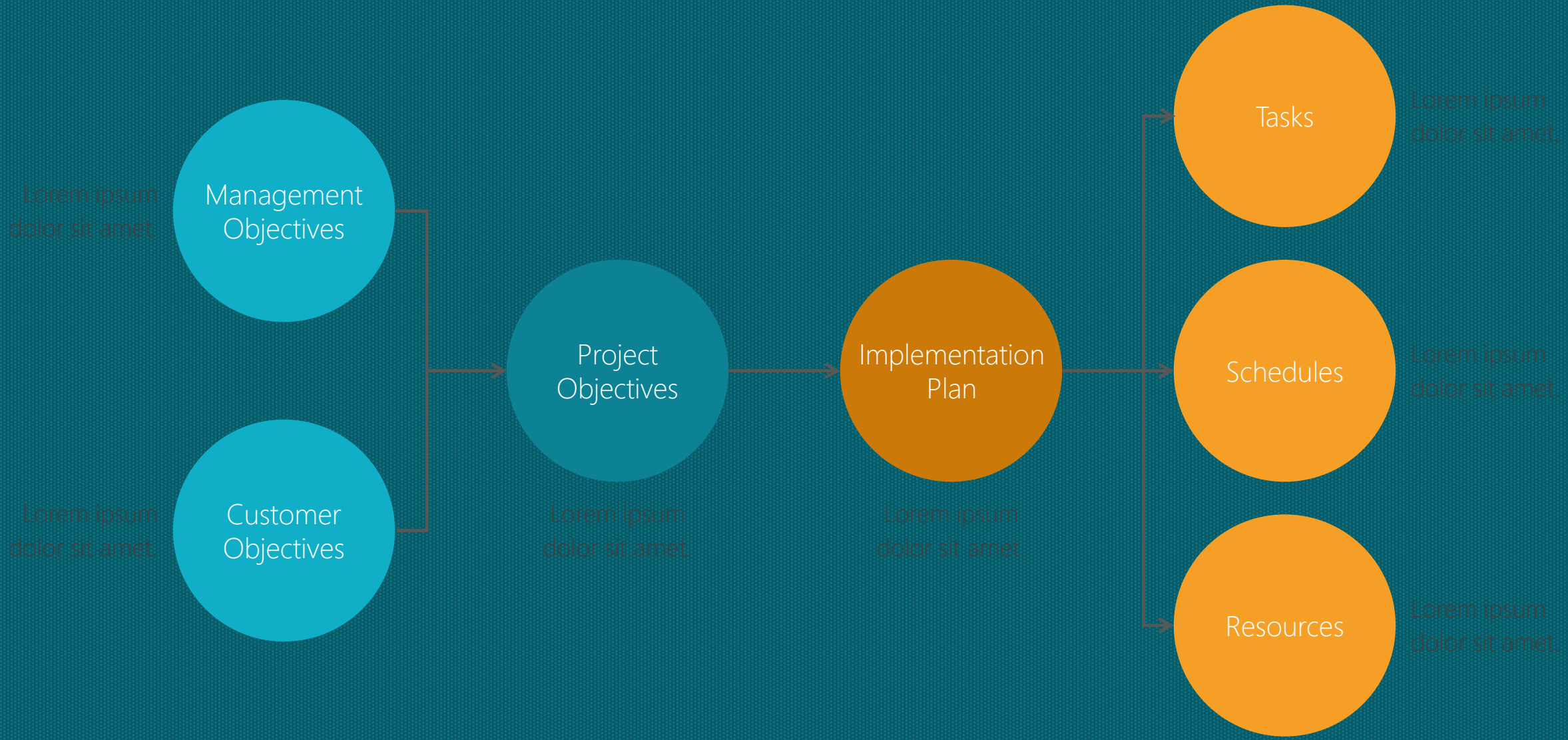

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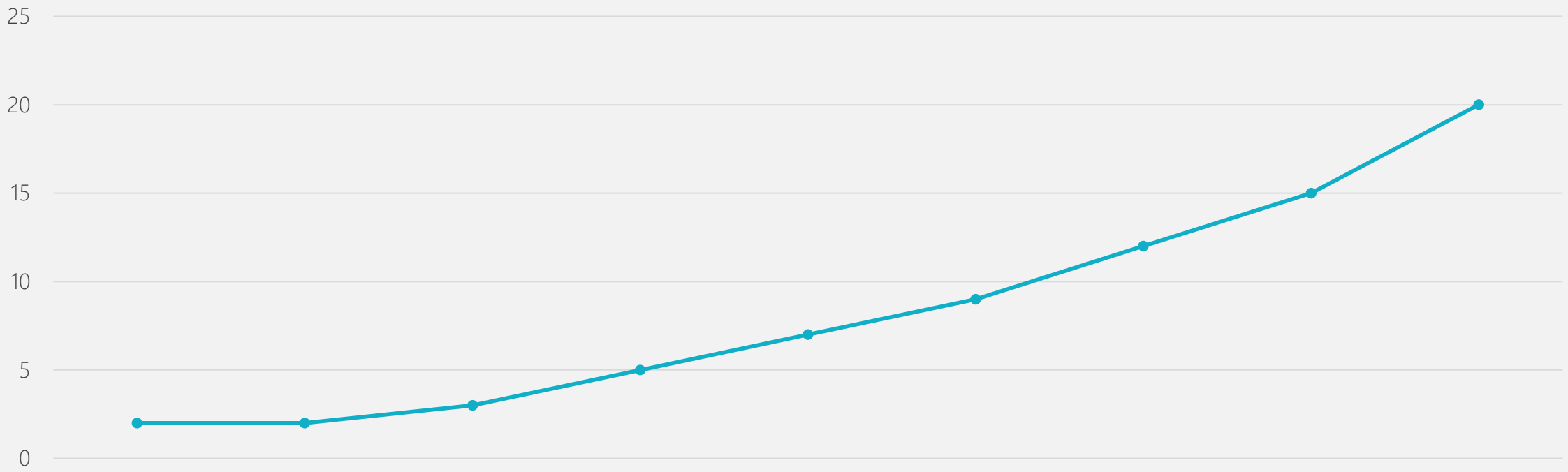

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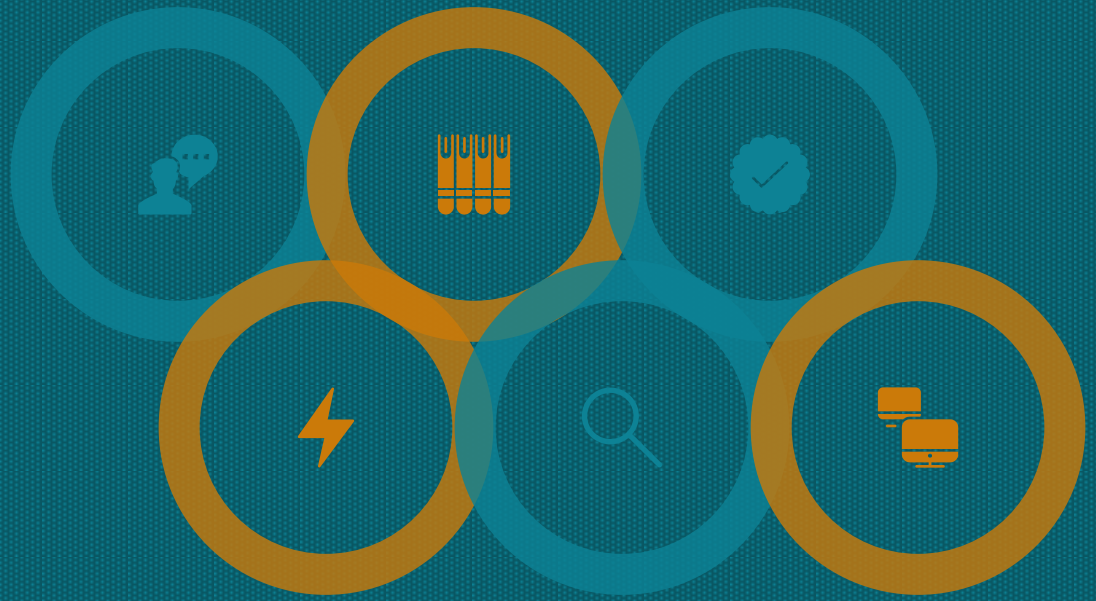

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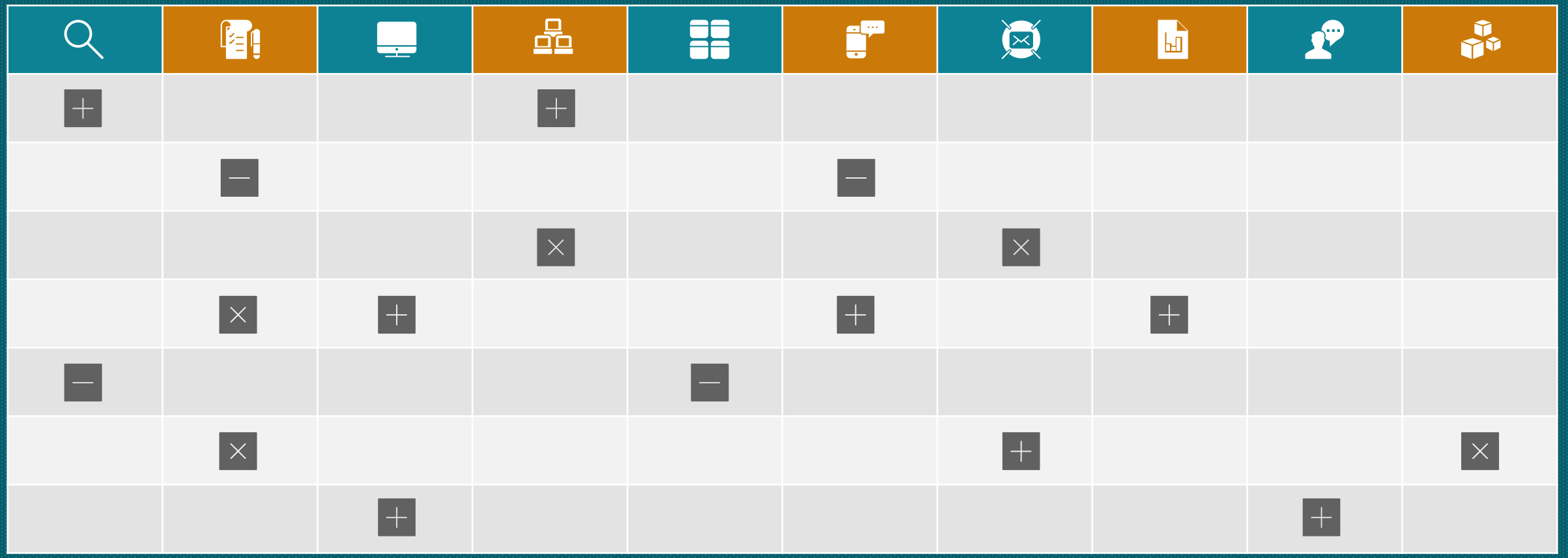

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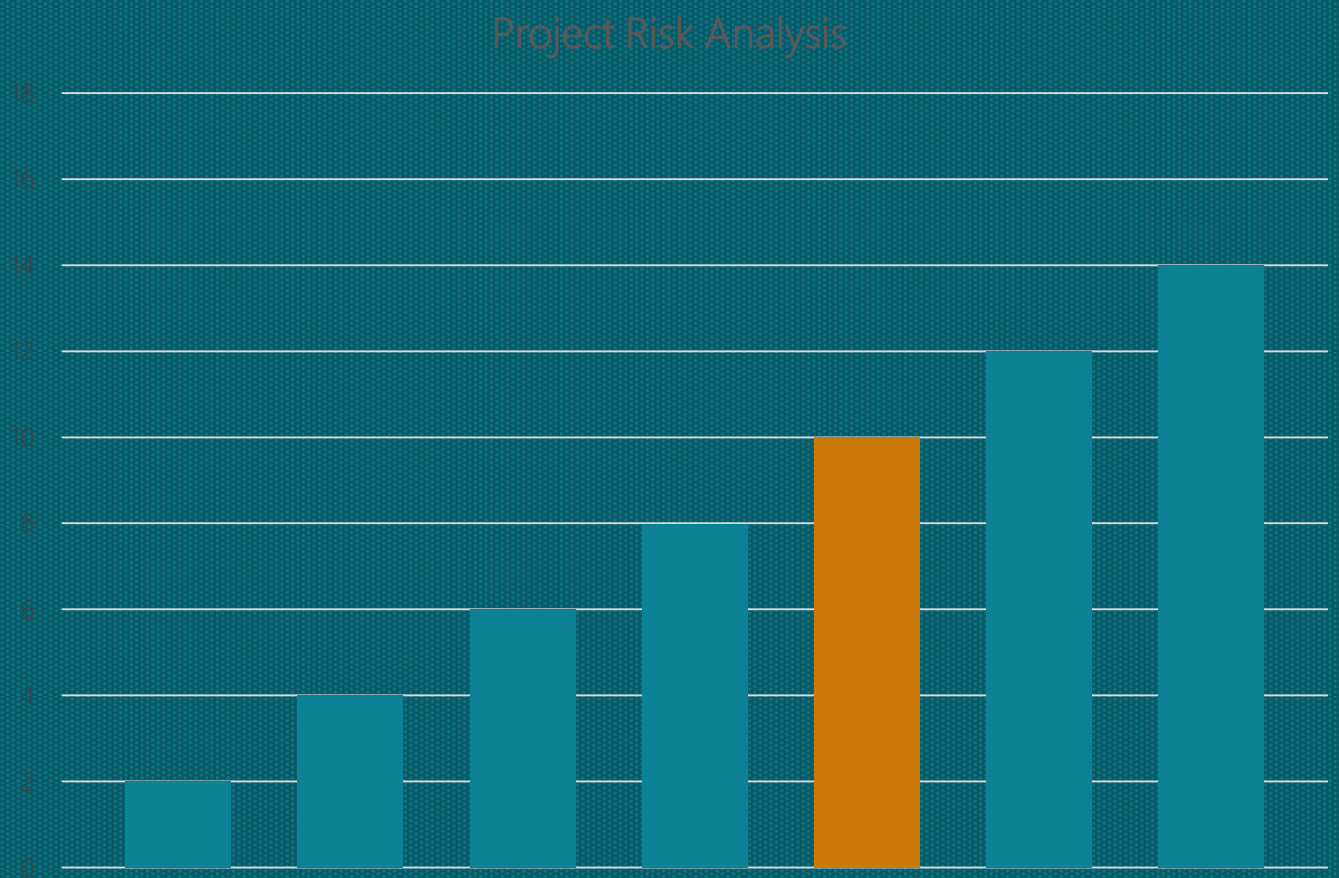
Project Analysis



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Thank You

Editing Data Slides

If you would like to modify the data in the graphs and chart included in this template, simply right click on the diagram and select *Edit Data in Excel*.

Excel will then open and you can edit the relevant data.