Tumore del polmone: le novità radioterapiche

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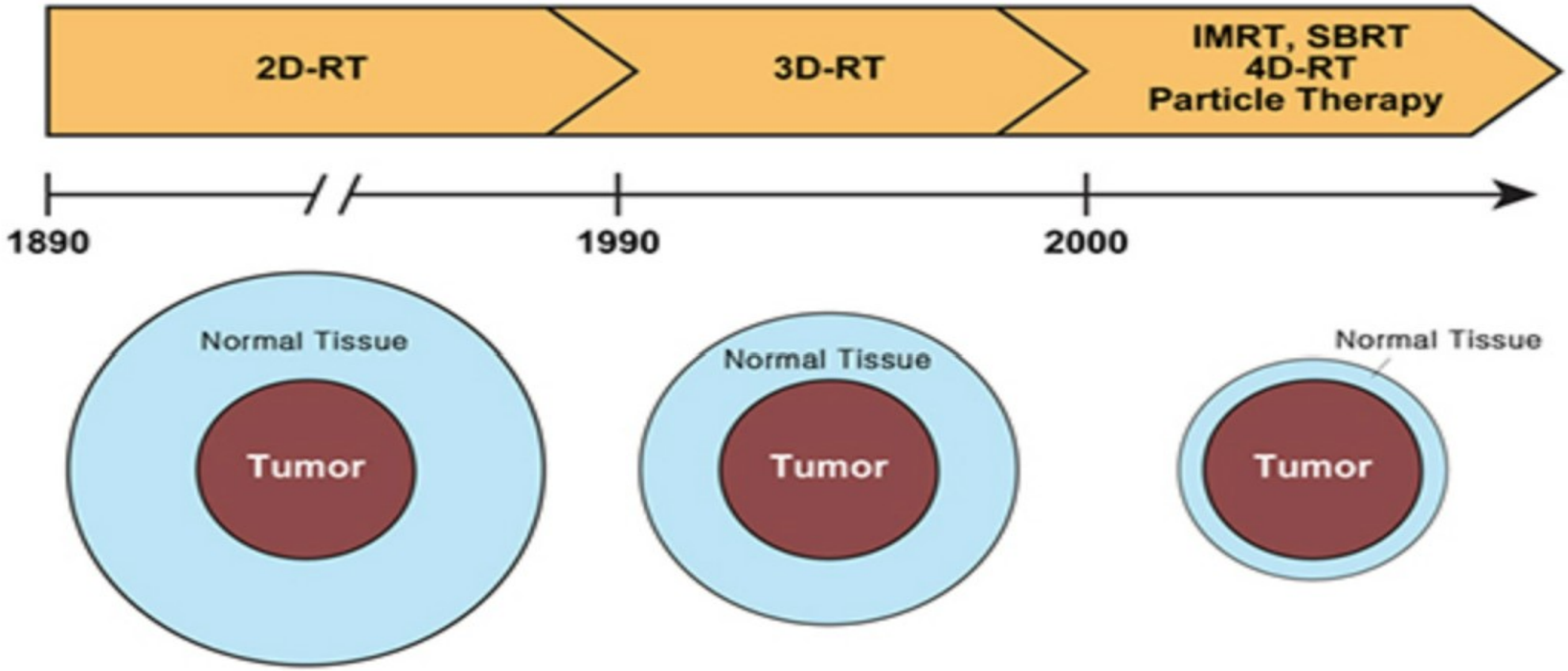
EVOLUTION OF MODERN RADIOTHERAPY

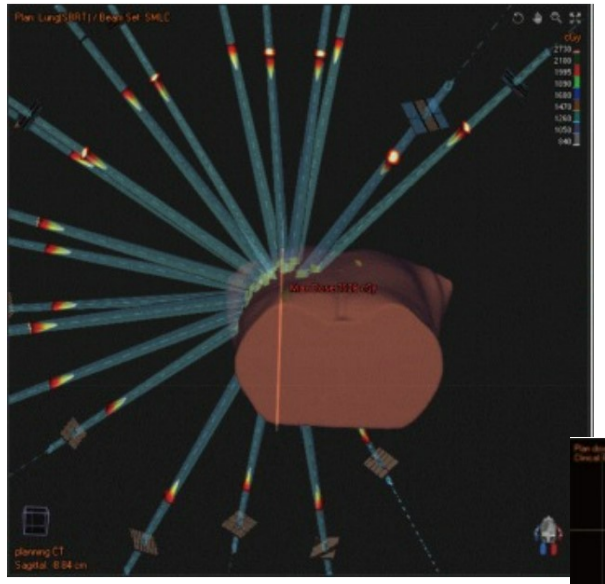


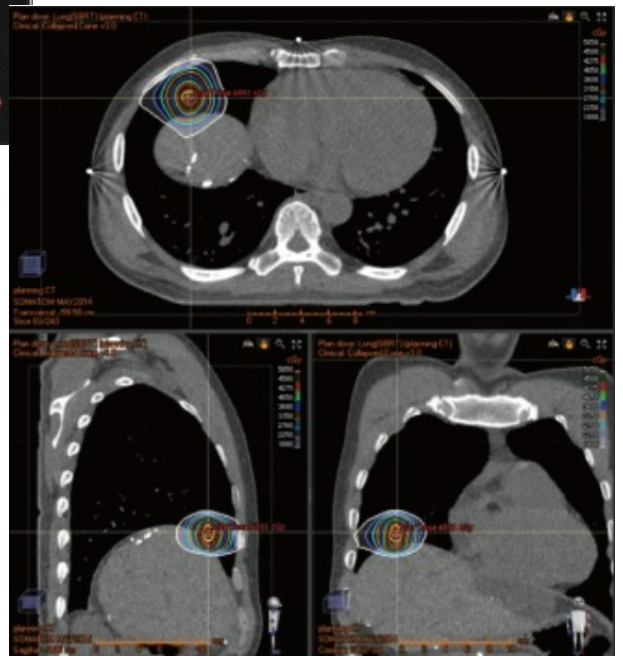
Modern radiotherapy is characterized by minimizing the volume of normal tissue being unnecessarily irradiated

WHAT IS SBRT ?

- Multiple convergent beams of RT aimed at target
- Requires rigid patient immobilization
- ***MUST account OR compensate for organ motion***
- Precise localization of target via stereotactic coordinate system
- Size-restriction for target

- Typically few-fraction (1 to 5) RT using **large** individual fraction doses
- ***High dose conformality, i.e., "tight around target"***
- Rapid dose fall-off from target to surrounding normal tissue.





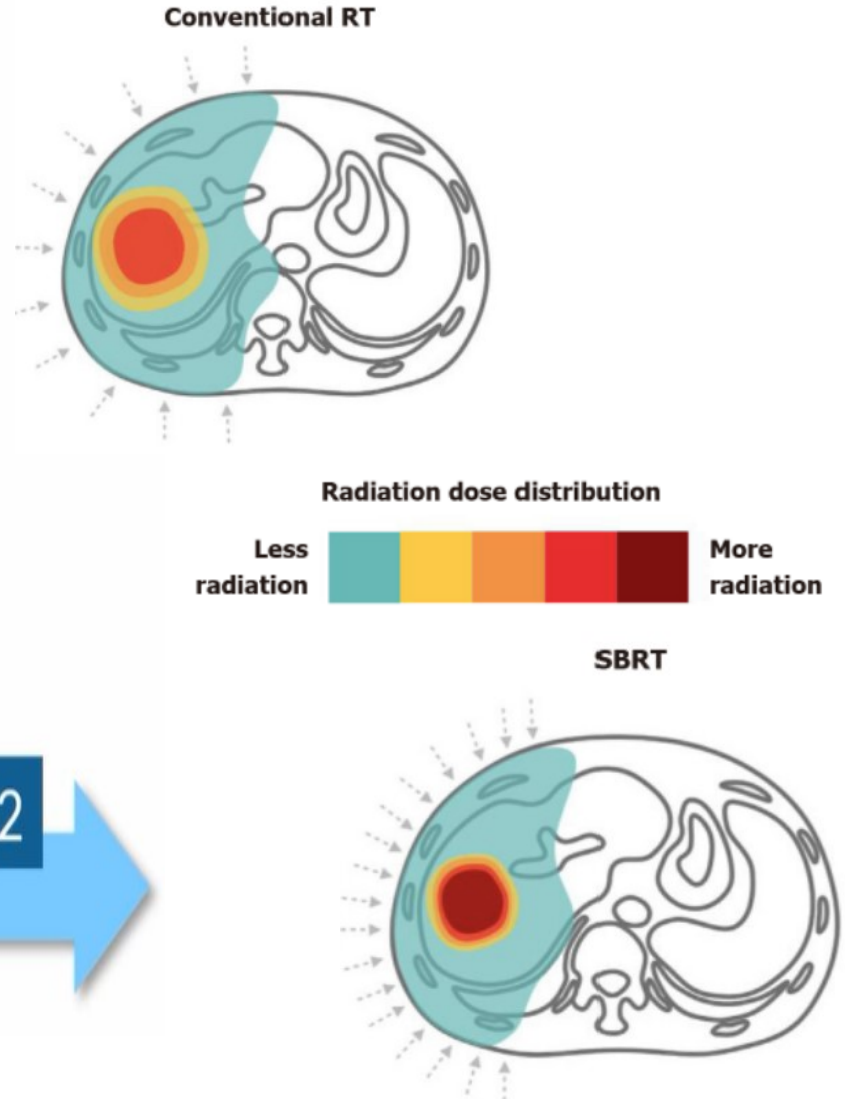
>25 years of lung SABR

Acta Oncologica Vol. 34, No. 6, pp. 861–870, 1995

STEREOTACTIC HIGH DOSE FRACTION RADIATION THERAPY OF EXTRACRANIAL TUMORS USING AN ACCELERATOR

Clinical experience of the first thirty-one patients

HENRIC BLOMGREN, INGMAR LAX, INGEMAR NÄSLUND and RUT SVANSTRÖM

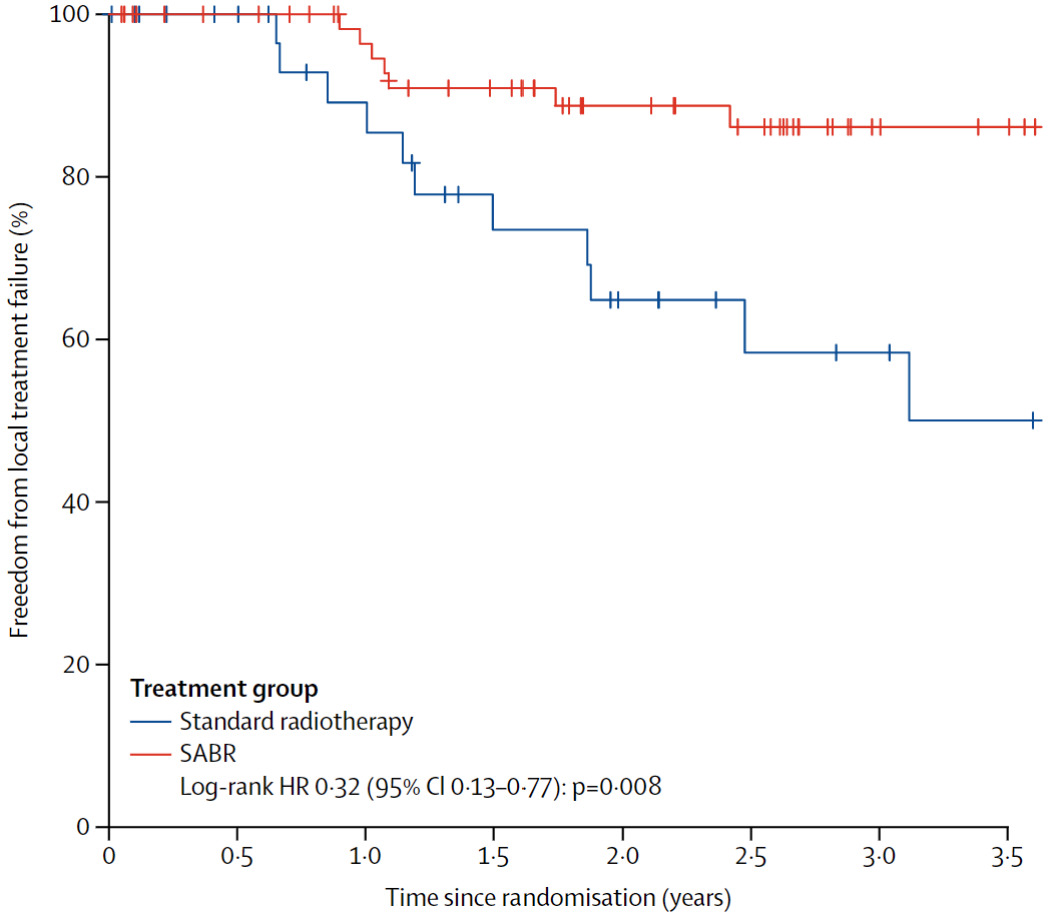


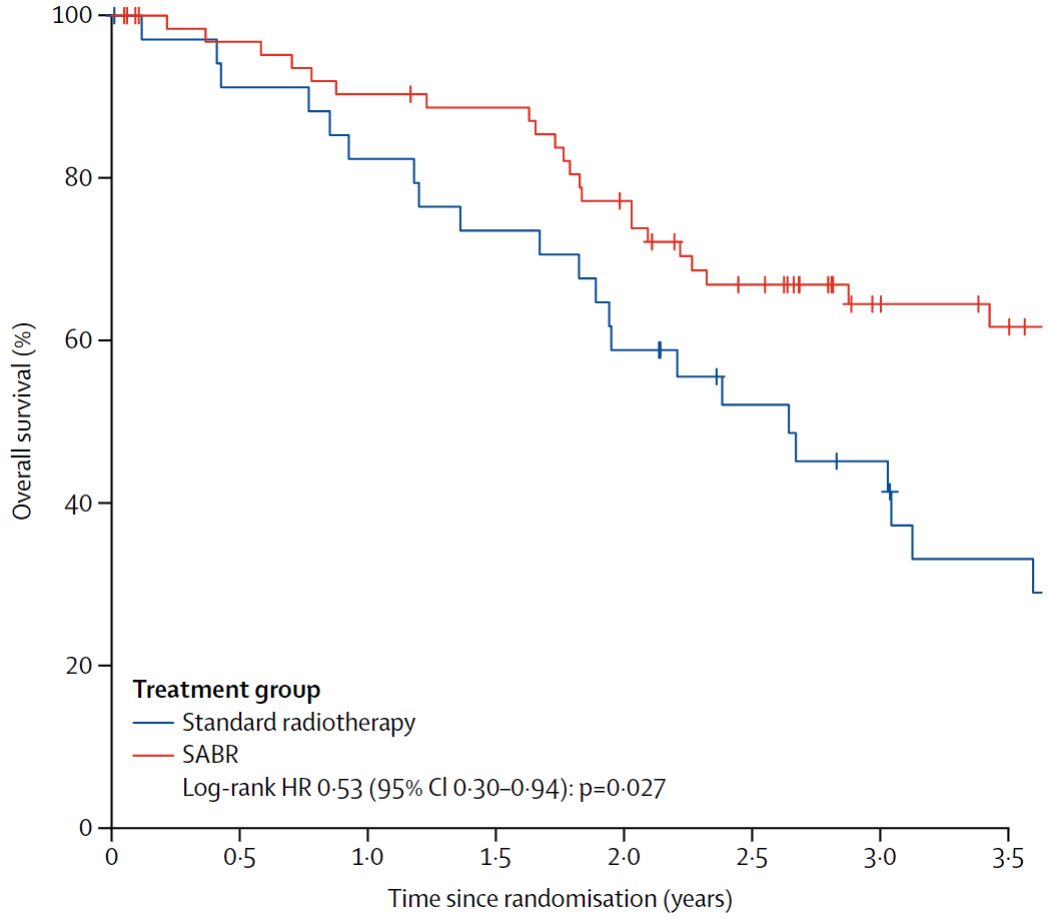
1995 → Major technical advances → Knowledge about high-risk cases → 2022

Large scale clinical experiences → Adoption in clinical guidelines

Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial

www.thelancet.com/oncology **Vol 20 April 2019**





ELSEVIER

STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR OPERABLE STAGE I NON–SMALL-CELL LUNG CANCER: CAN SBRT BE COMPARABLE TO SURGERY?

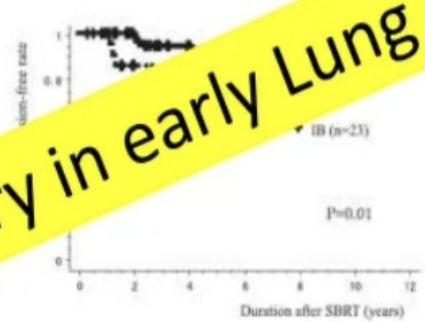
HIROSHI ONISHI, M.D.,* HIROKI SHIRATO, M.D.,† YASUSHI NAGATA, M.D.,‡ MASAHIRO HI... M.D.,§

2009

Can SBRT replace Surgery in early Lung cancers ??

Table 1. Patient characteristics

Number (14 institutions)	87
Male	63
Female	24
Age (y), median (range)	74 (43–87)
ECOG performance status	
0	51
1	
2	
Histology	
Adenocarcinoma	
Squamous cell carcinoma	25
Other	8
Stage	
IA	64
IB	23
Tumor di... (mm), m... (range)	25 (7–50)
IA	21
IB	39
Chronic lung disease	
Positive	38
Negative	49



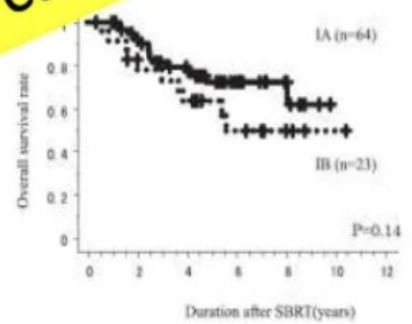


Table 3. Comparison of 5-y overall survival rate between surgical series and SBRT

Clinical stage	United States (1)	Japanese National Cancer Center (2)	Japanese National Survey (3)	SBRT
IA	61	71	77	76
IB	40	44	60	64

LC (5 yrs) → **92%** (IA) **73%** (IB)
Pulmonary complications > Gr 2 seen in 1 patient (1.1%)

Speaking of randomized trials...

Surgery vs. SABR in operable ES-NSCLC

- At least 4 prospective randomized trials of surgery vs. SABR have **failed** to complete accrual
- SABRTooth study: Pre-existing **treatment preferences** are a barrier to recruitment & randomization
- Other RCTs (e.g. VALOR, STABLE-MATES) are **ongoing**

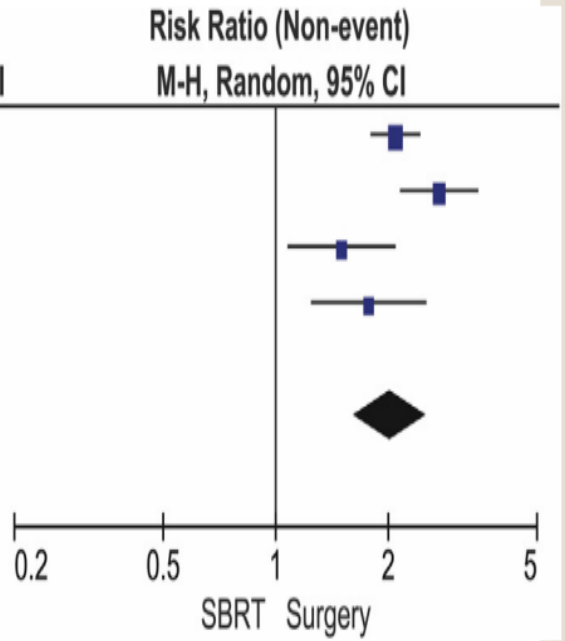
Oncologic Outcomes of Surgery Versus SBRT for Non–Small-Cell Lung Carcinoma: A Systematic Review and Meta-analysis

Five-Year OS After Surgery and SBRT for Comparative Cohort Studies

	SBRT		Surgery			Risk Ratio (Non-event)
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Crabtree 2014	38	151	294	458	32.5%	2.09 [1.79, 2.44]
Hamaji 2015	42	104	323	413	26.7%	2.74 [2.15, 3.48]
Matsuo 2014	46	115	39	65	21.0%	1.50 [1.08, 2.09]
Nakagawa 2014	15	35	124	183	19.8%	1.77 [1.24, 2.53]
Total (95% CI)		**405**		**1119**	**100.0%**	**2.03 [1.61, 2.55]**
Total events	141		780			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 9.43$, $df = 3$ ($P = 0.02$); $I^2 = 68\%$

Test for overall effect: $Z = 6.08$ ($P < 0.00001$)



Surgery has better OS than SBRT but…. retrospective data

Clinical Lung Cancer May 2021

Revised STARS

Single-arm prospective trial with a prespecified matched comparison to surgery

- Operable patients with stage I NSCLC (diameter ≤3 cm)
- PET-CT mandatory, EBUS performed in >90% (!)

- SABR (peripheral) 54 Gy @ 3 fx
- SABR (central) 50 Gy @ 4 fx (iGTV: SIB to 60 Gy)

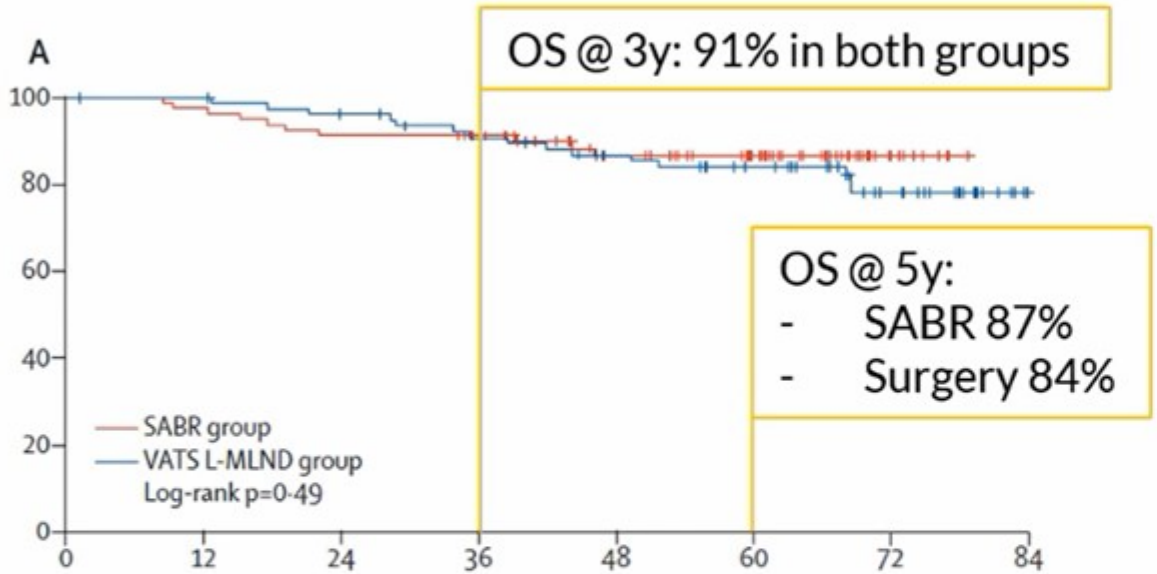
- Primary endpoint OS @ 3 years

Propensity-matching analysis using a prospective institutional database of stage I NSCLC patients undergoing VATS L-MLND

Lancet Oncol 2021; 22: 1448-57

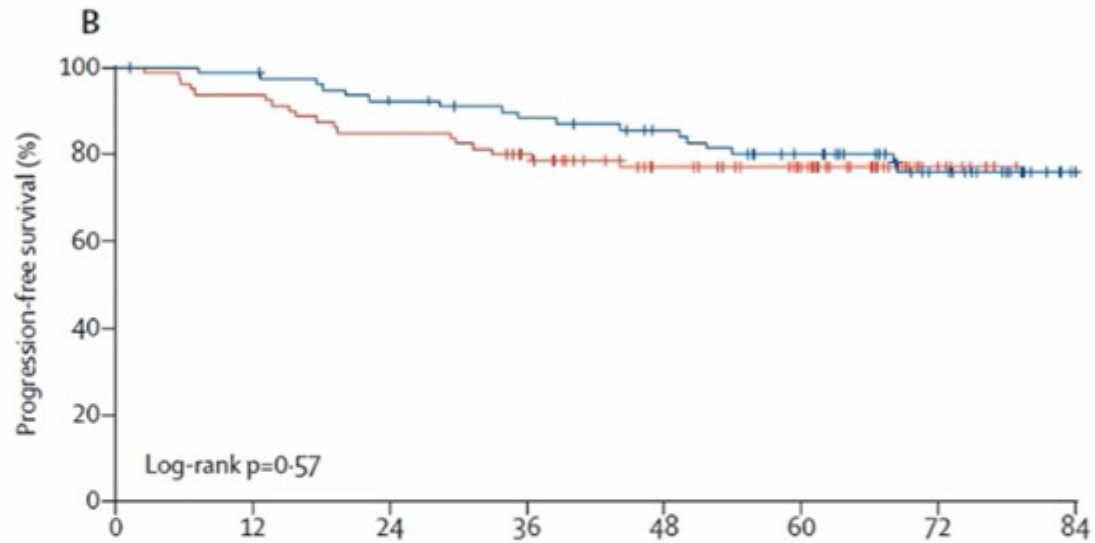
Revised STARS

Single-arm prospective trial with a prespecified matched comparison to surgery



OS @ 3y: 91% in both groups

OS @ 5y:
- SABR 87%
- Surgery 84%



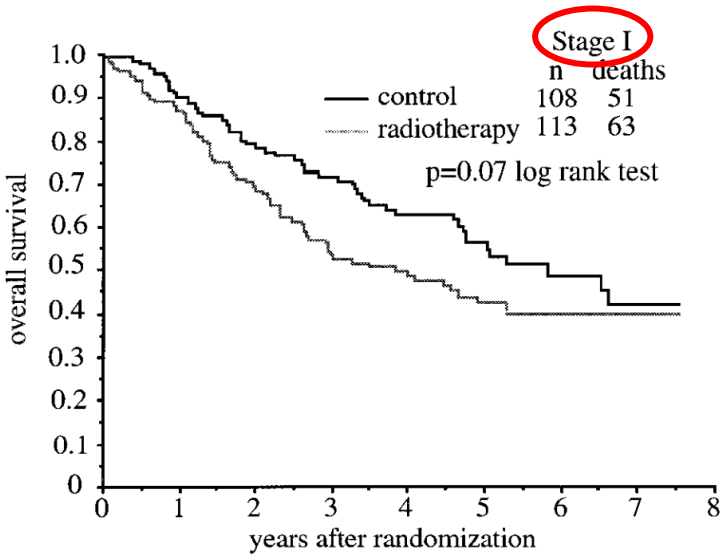
Number at risk (number censored)								
SABR group	80 (0)	78 (0)	73 (0)	69 (4)	51 (15)	39 (12)	11 (28)	..
VATS L-MLND group	80 (0)	79 (1)	74 (2)	68 (2)	61 (4)	54 (5)	37 (14)	..
SABR group	80 (0)	75 (0)	68 (0)	60 (4)	45 (13)	35 (10)	9 (26)	..
VATS L-MLND group	80 (0)	78 (1)	71 (2)	66 (2)	60 (4)	51 (5)	35 (14)	..

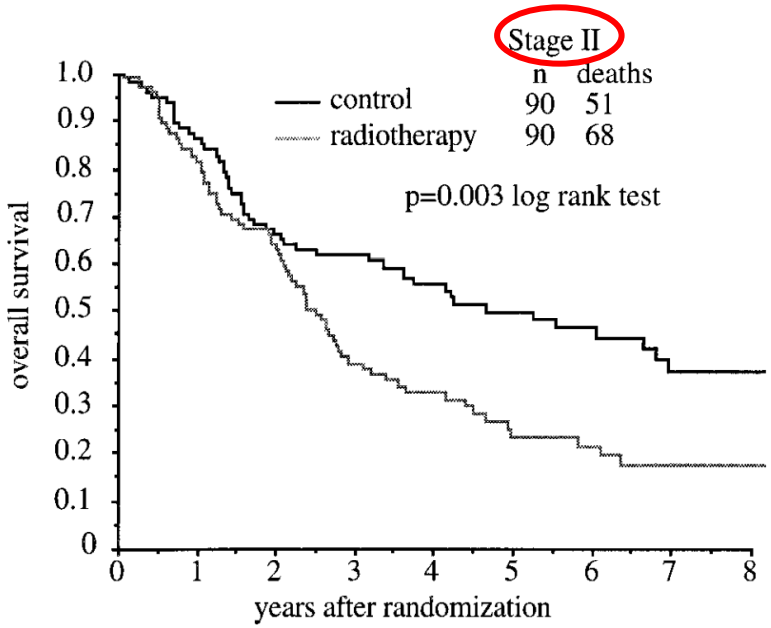
«Long-term survival after SABR is **non-inferior** to VATS L-MLND for operable stage IA NSCLC. SABR remains promising for such cases but **multidisciplinary management** is strongly recommended.»

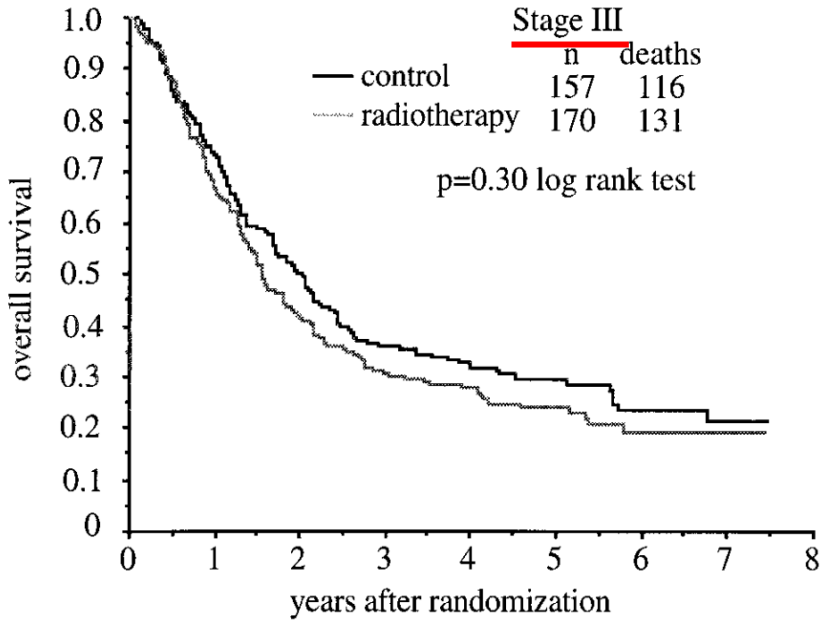
Lancet Oncol 2021; 22: 1448-57

...after surgery...RT?

A Controlled Study of Postoperative Radiotherapy for Patients with Completely Resected Nonsmall Cell Lung Carcinoma







RT detrimentale per lo stadio I e II

Necessità di terapia adiuvante per lo stadio III

CANCER July 15, 1999 / Volume 86 / Number 2

...after surgery...RT?

VIRTUAL 2020 ESMO congress

THE LATEST ADVANCES IN ONCOLOGY

2020

LUNG ART phase III Trial

Study design

(IFCT-0503, UK NCRI, SAKK)

Trial registry: NCT00410683

Completely resected NSCLC with N2 histo/ cytologically proven nodal involvement

R

Pre-op and/or Post-op CT

1:1 randomization

Control

Conformal PORT (54 Gy/5,5 wks)

Stratification factors : Center, Administration of CT (no CT vs Post-op CT vs pre-op CT alone), Histology (SCC vs other), Extent of mediastinal lymph node involvement (0 vs 1 vs 2+), use of pre-treatment PET-scan (yes/no)

Primary end-point: Disease-free survival

Secondary end-points: Overall survival, patterns of relapse, local failure, second cancers, and treatment-related toxicity

SCIENCE: 19-21 SEPTEMBER 2020 / EDUCATION: 16-18 OCTOBER 2020

...after surgery...RT?

VIRTUAL 2020 ESMO congress

THE LATEST ADVANCES IN ONCOLOGY

2020

VIRTUAL 2020 ESMO congress

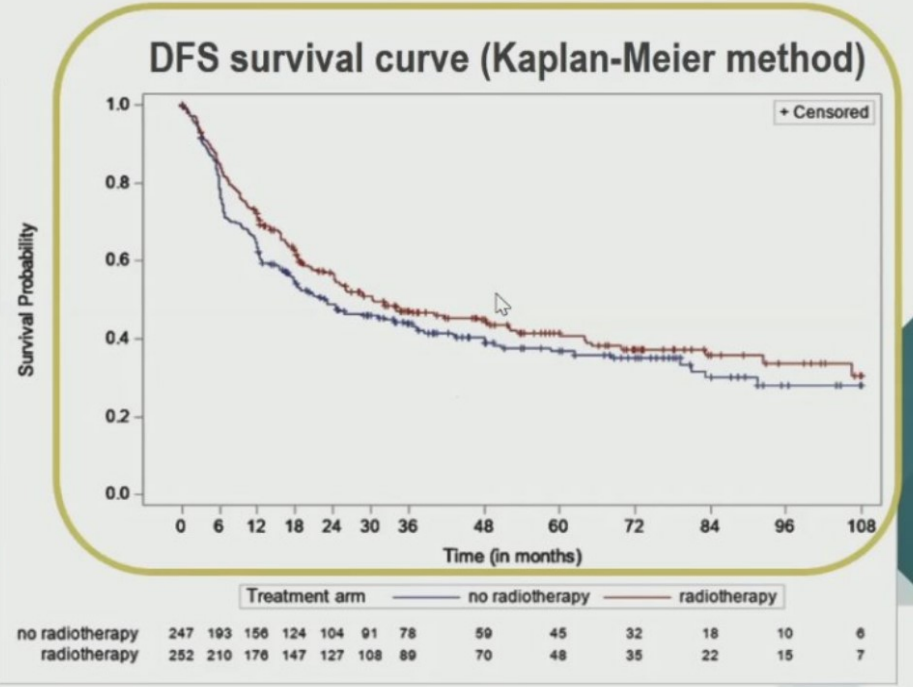
Disease-Free Survival 1/3 (Primary Endpoint; ITT)

Main analysis (Adjusted Cox Model)

HR = 0.85
95% CI = [0.67;1.07]
p value = 0.16

	Control	PORT
Median DFS	22.8 mo (95% CI = [17;37])	30.5 mo (95% CI = [24;49])
3-yr DFS	43.8% (95% CI = [37;51])	47.1 % (95% CI = [40;54])

95%CI = 95% bilateral Confidence Interval



SCIENCE: 19-21 SEPTEMBER 2020 / EDUCATION: 16-18 OCTOBER 2020

...after surgery...RT?

DFS components (First Event)

	Control	PORT
All DFS events*	152	144
Mediastinal relapse	70 (46.1 %)	36 (25.0%)
Brain metastasis	27 (17.8%)	34 (23.6%)
Other metastasis	71 (46.7%)	71 (49.3%)
Death	8 (5.3%)	21 (14.6%)

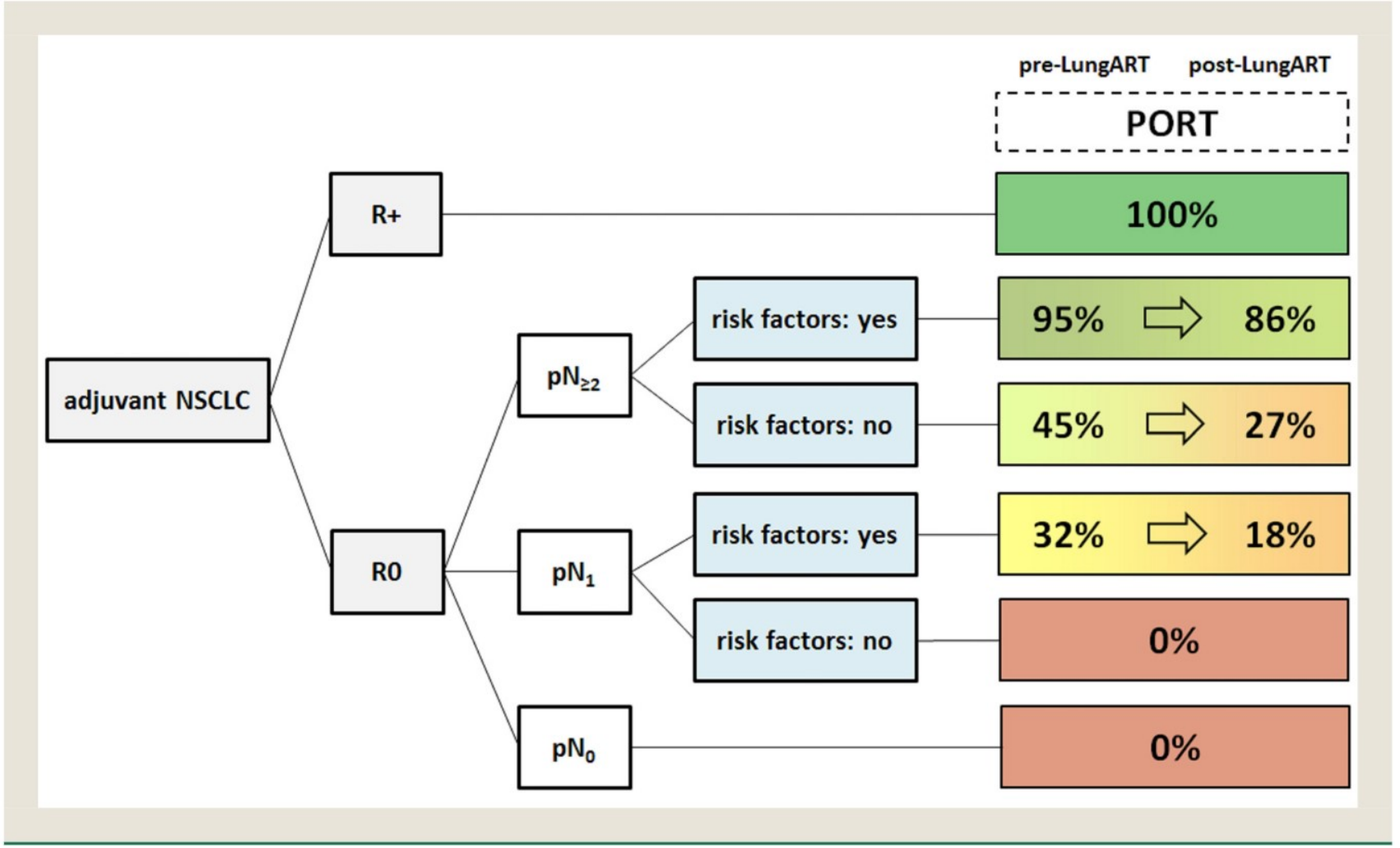
Causes of death

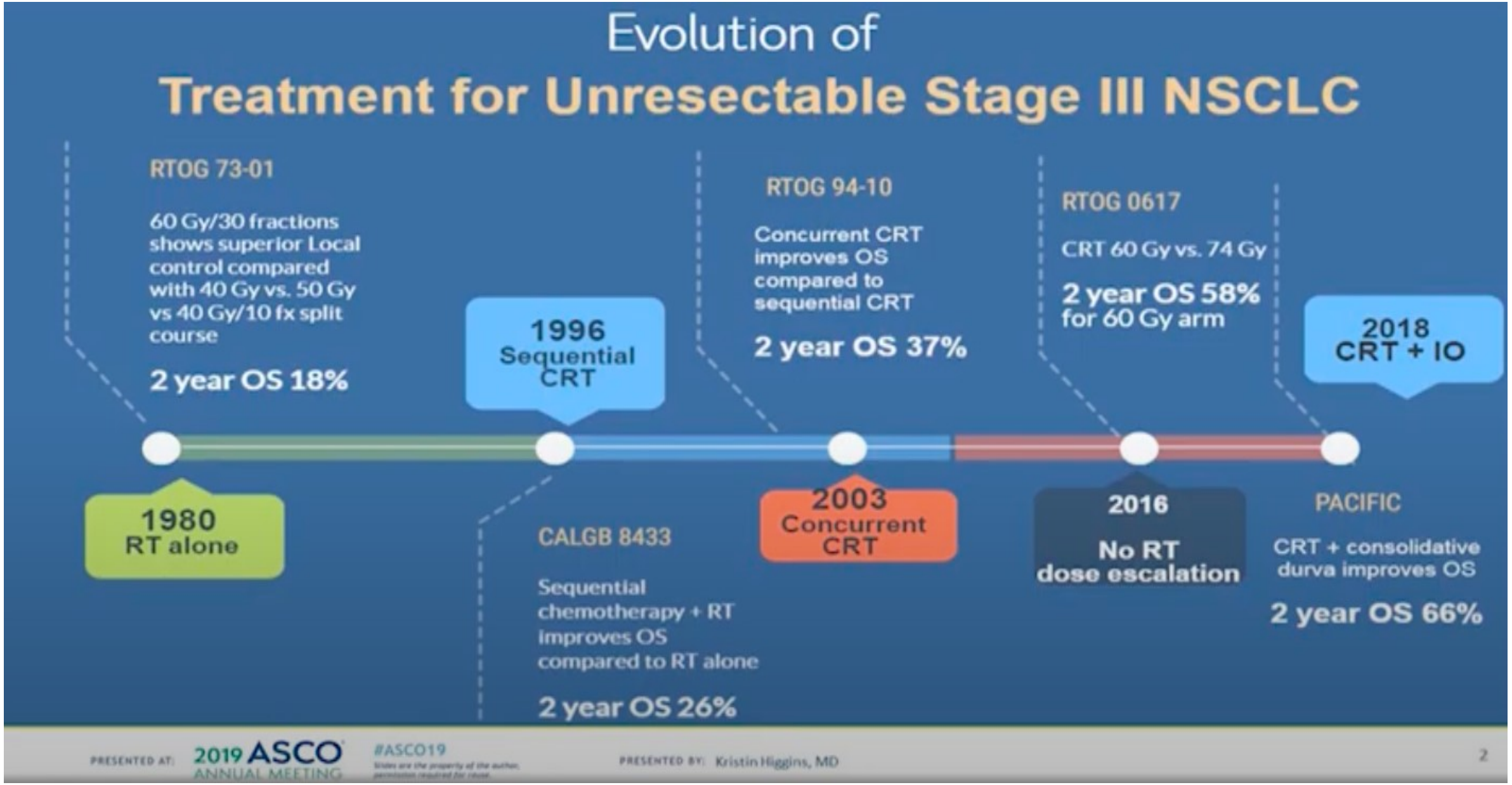
	Control arm (n = 249)	PORT arm (n = 252)
Deaths	102 (41.5%)	99 (39.6%)
Cause of death		
- Progression or recurrence	87 (86.1%)	68 (69.4%)
- Cardio-pulmonary	2 (2.0%)	16 (16.2%)
- Second primary	1 (1.0%)	5 (5.1%)
- RT or CT related toxicity	0 (0%)	3 (3.0%)
- Other	11 (10.9%)	6 (6.1%)
- Unreported	1	1

PORT technique†		
Three-dimensional conformal radiotherapy	201/226 (89%)	..
Intensity-modulated radiotherapy	25/226 (11%)	..
Missing information	15	..

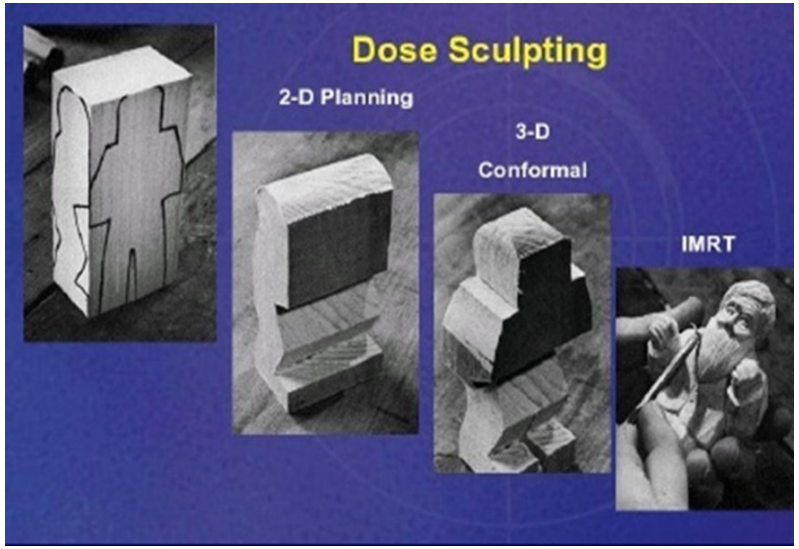
Interpretation Lung ART evaluated 3D conformal PORT after complete resection in patients who predominantly had been staged using (^{18}F-FDG PET-CT and received neoadjuvant or adjuvant chemotherapy. 3-year disease-free survival was higher than expected in both groups, but PORT was not associated with an increased disease-free survival compared with no PORT. Conformal PORT cannot be recommended as the standard of care in patients with stage IIIAN2 NSCLC.

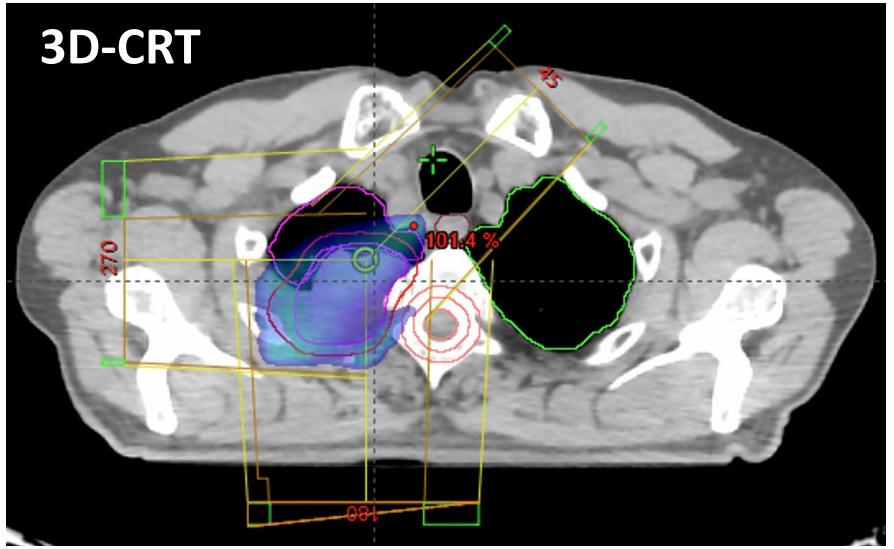
Role of Postoperative Radiotherapy in the Management for Resected NSCLC – Decision Criteria in Clinical Routine Pre- and Post-LungART

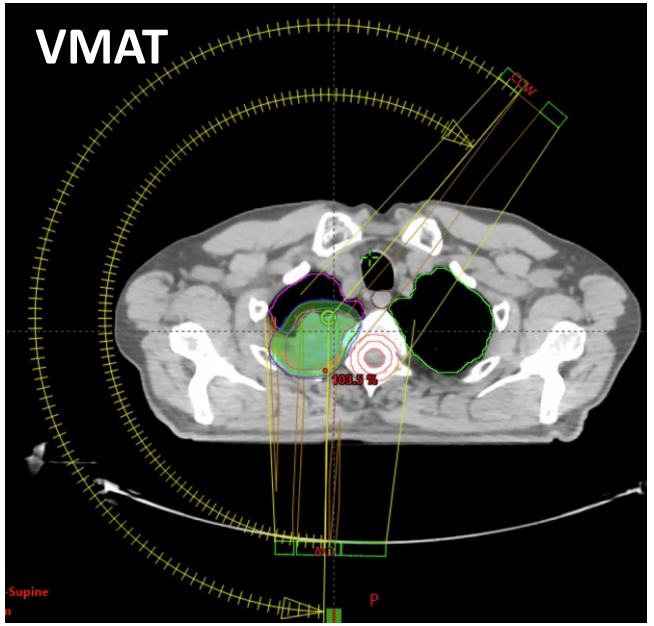


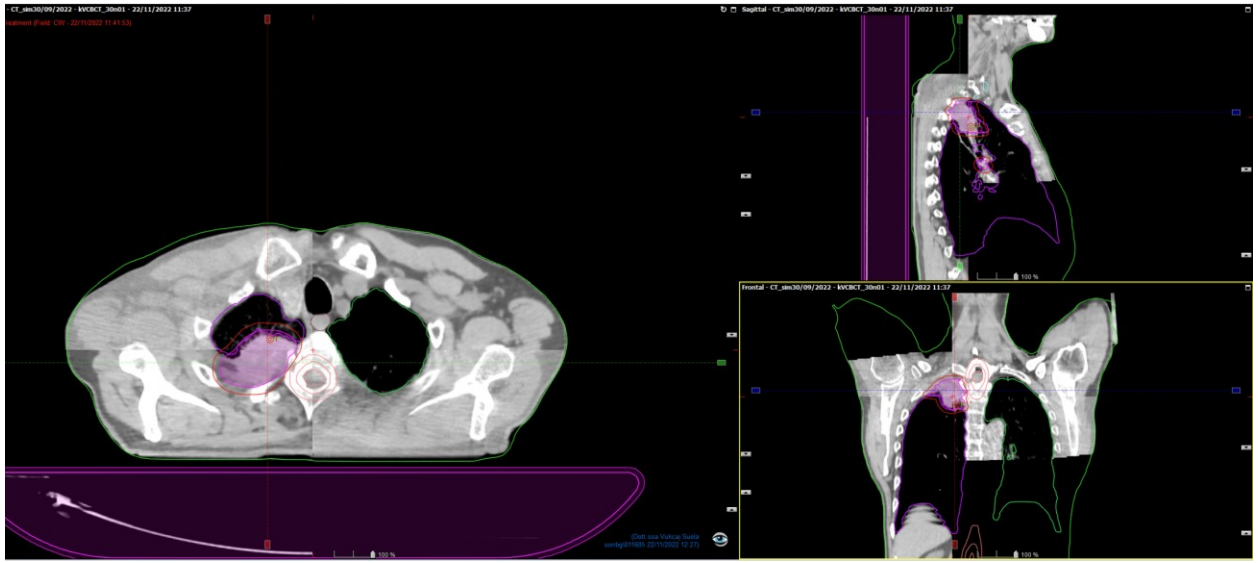

Evolution of
Treatment for Unresectable Stage III NSCLC
RTOG 73-01
60 Gy/30 fractions shows superior Local control compared with 40 Gy vs. 50 Gy vs 40 Gy/10 fx split course
2 year OS 18%
1980
RT alone
1996
Sequential CRT
CALGB 8433
Sequential chemotherapy + RT improves OS compared to RT alone
2 year OS 26%
RTOG 94-10
Concurrent CRT improves OS compared to sequential CRT
2 year OS 37%
2003
Concurrent CRT
RTOG 0617
CRT 60 Gy vs. 74 Gy
2 year OS 58% for 60 Gy arm
2016
No RT dose escalation
2018
CRT + IO
PACIFIC
CRT + consolidative durva improves OS
2 year OS 66%
PRESENTED AT: 2019 ASCO ANNUAL MEETING
#ASCO19
PRESENTED BY: Kristin Higgins, MD
2

Scoperte tecnologiche ⟷ Conquiste cliniche







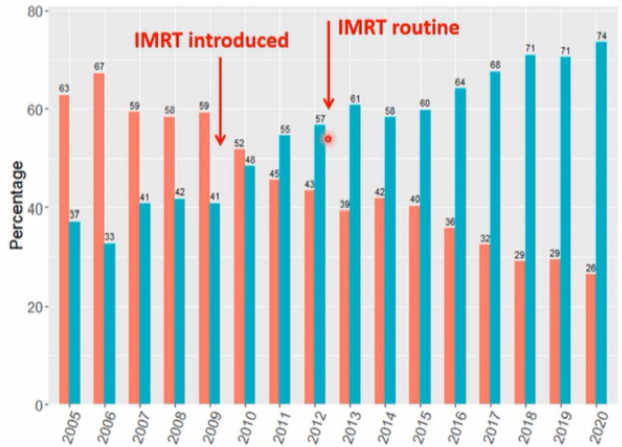


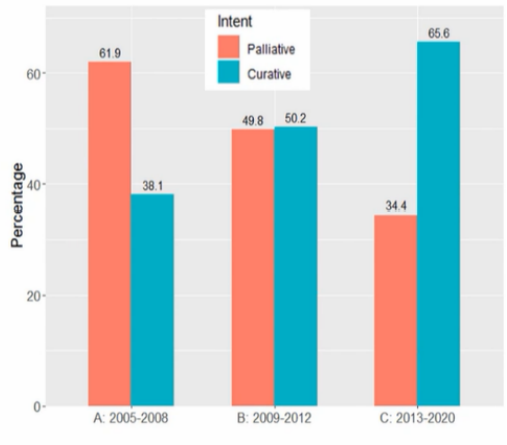
- ✓ maggior accuratezza nella definizione del target
- ✓ maggior accuratezza nell'immobilizzazione del pz.
- ✓ maggior accuratezza geometrica

✓ trattamenti «*image-guided*» sia nella definizione del target sia nell'erogazione del fascio

Impact of introducing IMRT on curative intent radiotherapy and survival for lung cancer

Proportion of patients receiving curative intent radiotherapy





Whole cohort, n= 12499

The introduction of IMRT was associated with more patients receiving curative-intent radiotherapy across all PS and stages of disease

Despite treating larger, more complex tumours and patients with poorer PS with curative-intent, a survival benefit was seen

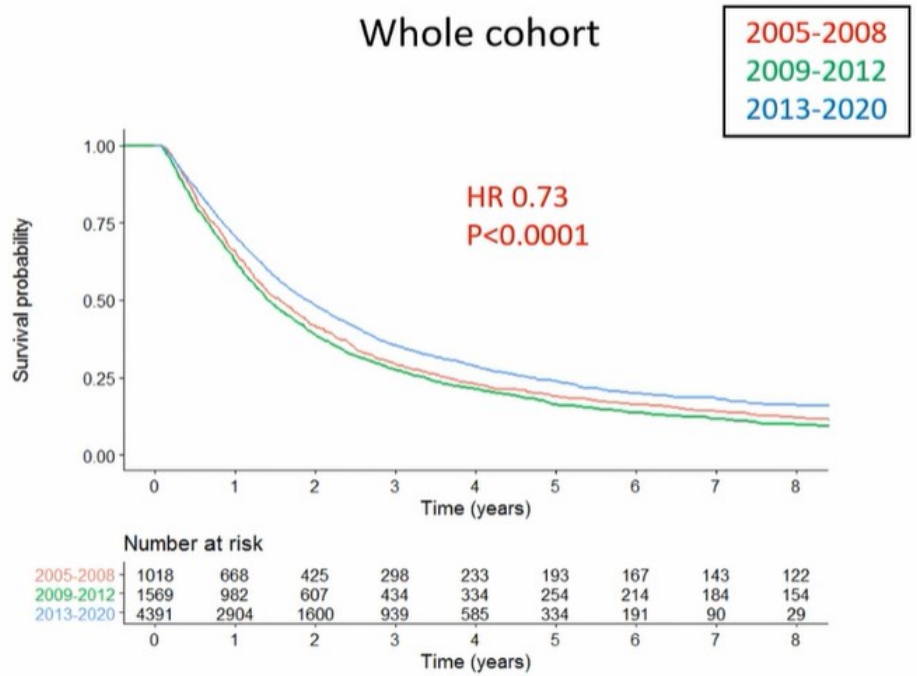
IMRT facilitates treatment of larger tumours so likely was a significant contributing factor to the changes observed

This study illustrates the scope of big data analysis, but is limited by missing data including data on systemic therapy

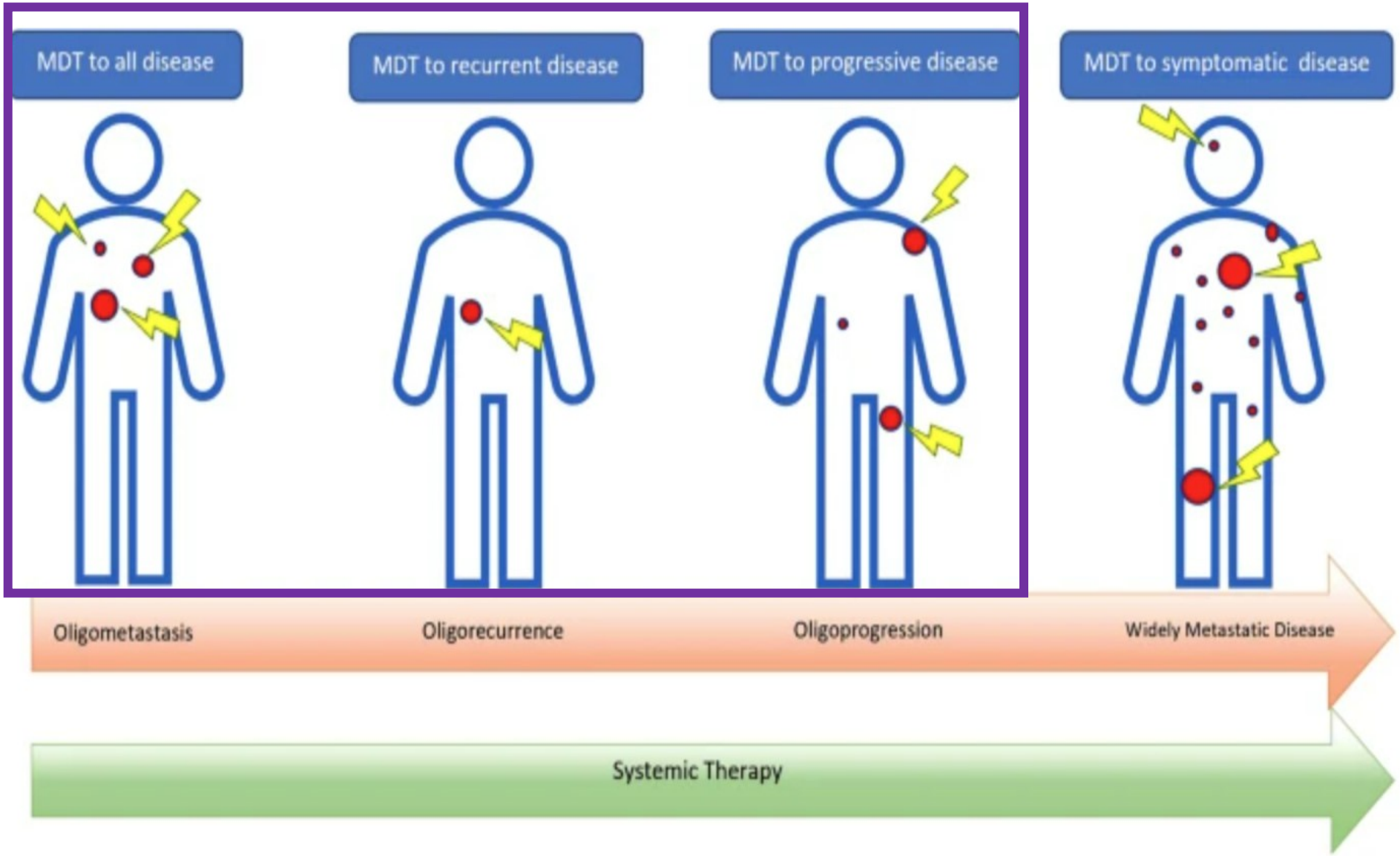
Other factors will have also contributed to improved survival

E.g. Improved staging, other advances in technical radiotherapy, systemic therapy

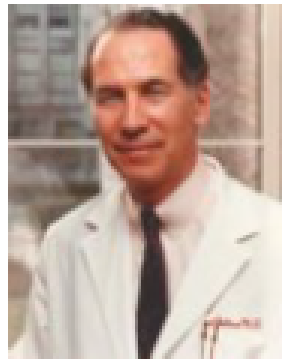
Results – patient survival



Stage IV... palliative RT?

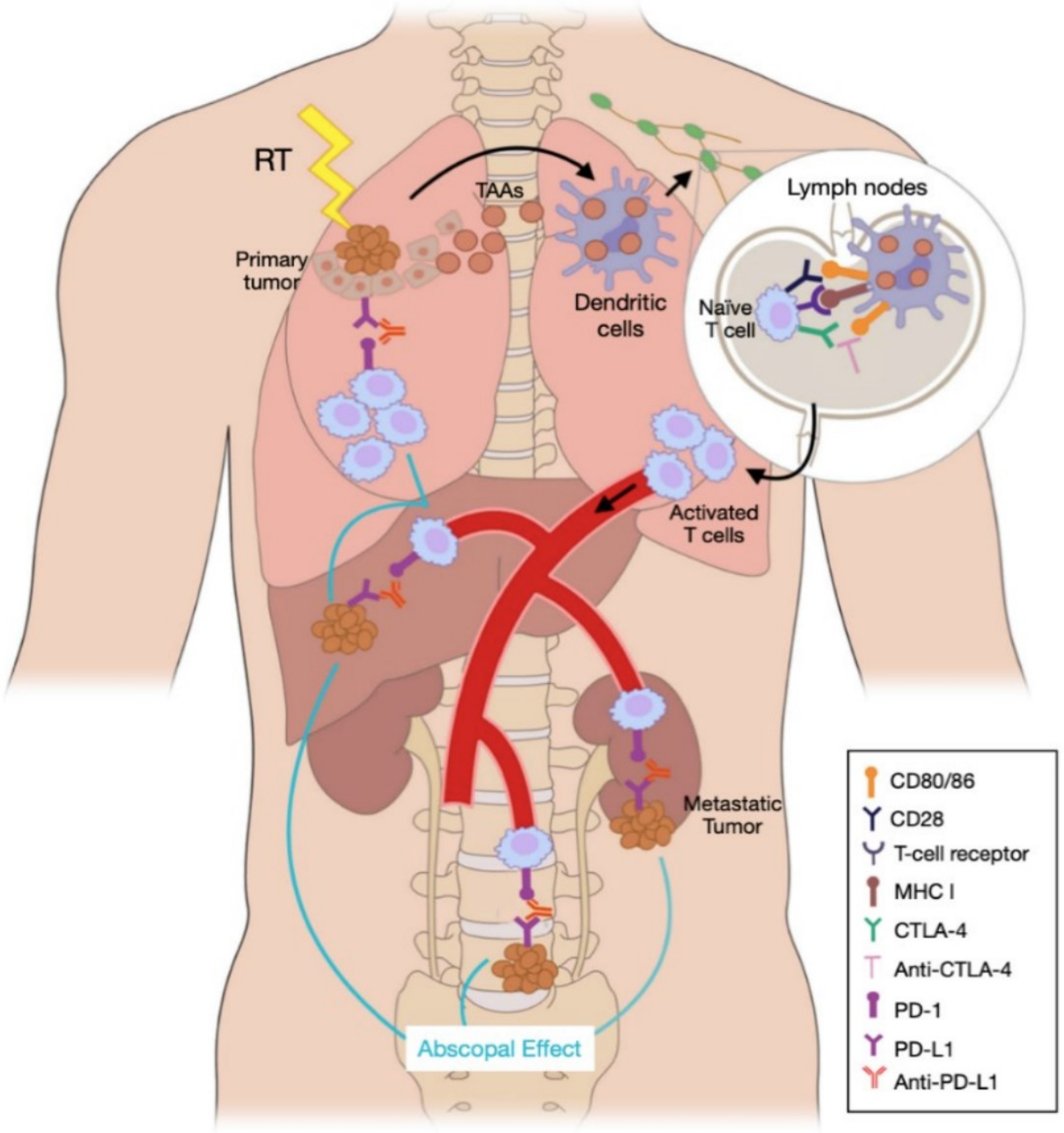


Oligometastatic concept



Greek root *"oligo"* meaning few

- ✓ First proposed by S. Hellmann and R. Weichselbaum in 1995
- ✓ Clinical condition of metastasis where tumors have restricted metastatic capacity
- ✓ Implications: local treatment of metastatic lesion is curative



RT potentiates the antitumour immune response through

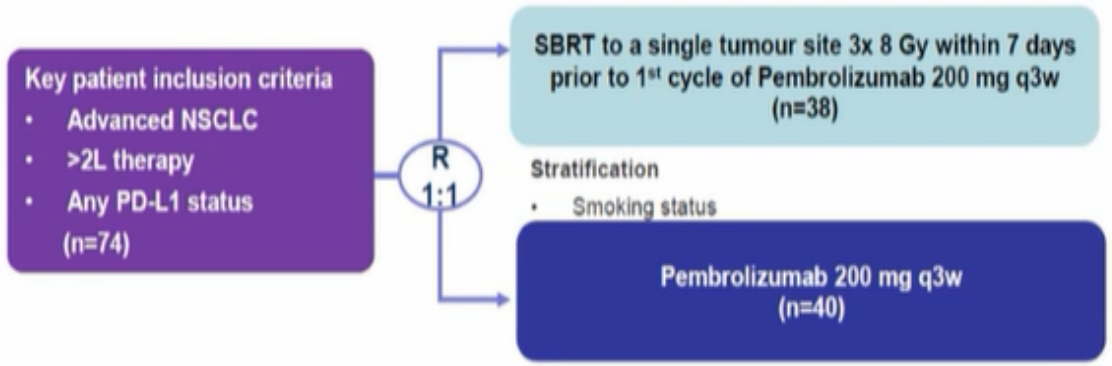
- Release of **tumour neo-antigens** from dying tumour cells
- Enhancement of MHC class I expression
- Upregulation of chemokines, cell-adhesion molecules and other immunomodulatory cell surface molecules

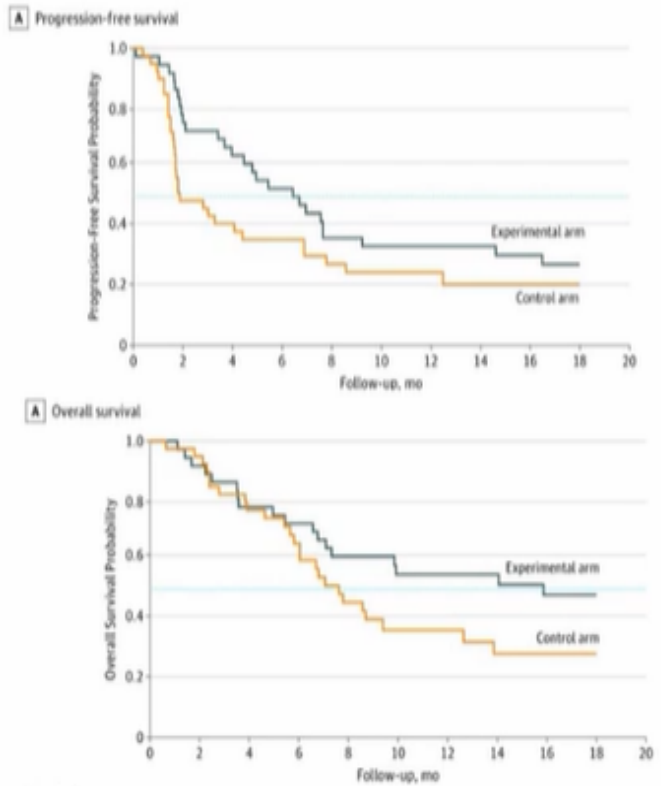
However the **microenvironement is typically immunosuppressive** and dampens down the immune response e.g. through the interaction between the PD1 and PDL1 receptors

PD-1 → Programed Death-1
PD-L1 → Programed Death Ligand-1

Opportunities for LAT+ Immunotherapy

Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non-Small Cell Lung Cancer: Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial





Median progression-free survival was 1.9 months vs 6.6 months

Median overall survival was 7.6 months vs 15.9 months

Adding radiotherapy to pembrolizumab immunotherapy significantly increased responses and outcomes in patients with metastatic non-small-cell lung cancer. These results warrant validation in a randomised phase 3 trial.

Theelen WSME A et al. Jama Oncol 2019

Optimize Local Therapy for Oligometastatic and Oligoprogressive Non–Small Cell Lung Cancer to Enhance Survival

Trial	Design	Histology	Population	Sample Size n	Follow-Up y	Comparison	Outcomes
Sheu et al	Retrospective	NSCLC	Oligometastatic disease (≤3 metastases not including the primary)	49	3.9	First-line chemotherapy or concurrent chemoradiation in all patients; maintenance therapy/observation vs SABR/surgery	Higher PFS and OS with local therapy on propensity-matched analysis
Gomez et al	Randomized	NSCLC	Oligometastatic disease (≤3 metastases not including the primary)	49	3.2	First-line chemotherapy in all patients; maintenance therapy/observation vs subsequent RT (62%) or surgery (4%) or both (24%)	Higher PFS and OS with local therapy
Iyengar et al	Randomized	NSCLC	Oligometastatic disease (≤6 lesions including the primary with ≤3 metastases in lung or liver)	29	0.8	First-line chemotherapy in all patients; maintenance chemotherapy vs SABR	Higher PFS with local therapy; incomplete follow-up for OS
Xu et al	Retrospective	*EGFR*m NSCLC	Oligometastatic disease (≤5 lesions excluding the primary)	145	3.2	First-line, first-generation TKI in all patients; maintenance therapy/observation vs subsequent RT, surgery, both, or RFA (liver metastases only)	Higher PFS and OS with local therapy to all sites of disease on propensity-matched analysis
Palma et al	Randomized	Mixed	Oligorecurrent disease (≤5 metastases)	99	4.3	Palliative standard of care vs SABR	Higher PFS and OS with local therapy
Wang et al	Randomized	*EGFR*m NSCLC	Oligometastatic disease (≤5 lesions excluding the primary with <3 metastases in any 1 organ)	133	2.0	Up-front RT followed by first-generation TKI vs up-front first-generation TKI	Higher PFS and OS with local therapy
Tsai et al	Randomized	NSCLC and breast cancer	Oligoprogressive disease (≤5 areas of progression) after ≥1 lines of systemic therapy	102	1.0	Palliative standard of care therapies vs SABR	Higher PFS with local therapy; findings significant in NSCLC but not in breast histology

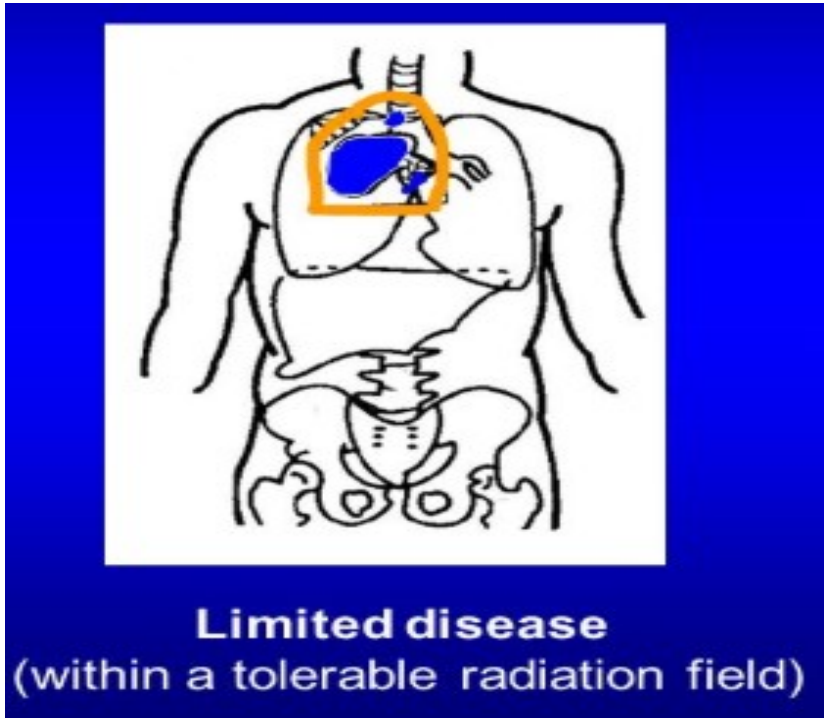
The addition of LAT to OPD improve:
-local control
-suppress secondary metastasis
-prolong PFS and OS

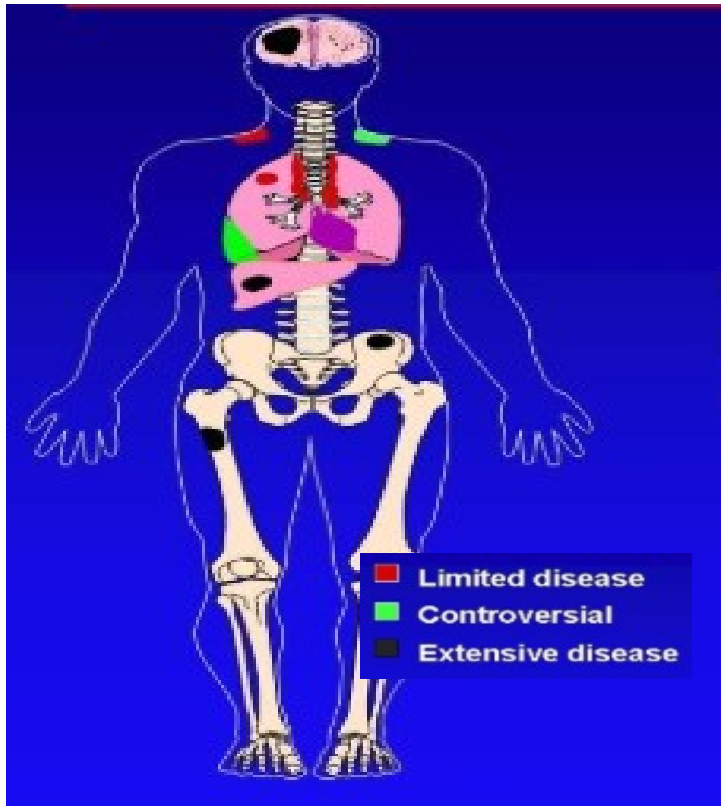
Limitations:
-retrospective study
-small sample size
-short follow up

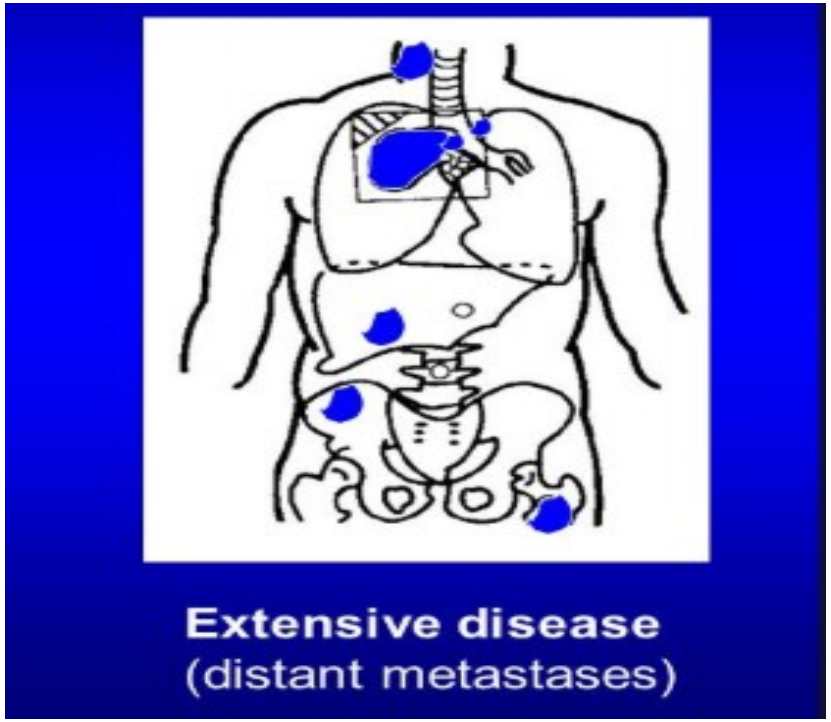
Ongoing Phase III Studies of Local Therapy Versus No Local Therapy for Oligometastatic or Oligoprogressive[a] NSCLC

Trial Name	ClinicalTrials.gov Identifier	Histology	Metastases	Systemic Therapy	Local Therapy	Primary Endpoint
OMEGA	NCT03827577	NSCLC	1–3	Chemotherapy, IO, targeted agents	RT, surgery, RFA	OS
SARON	NCT02417662	NSCLC	1–5	Per physician discretion	RT	OS
NRG LU002	NCT03137771	NSCLC	1–3	Chemotherapy or IO	RT	PFS (phase II), OS (phase III)
CORE	NCT02759783	NSCLC, breast cancer, prostate cancer	1–3	Per physician discretion	RT	PFS
OITROLC	NCT02076477	NSCLC	1–5	Chemotherapy	RT	ORR
SABR-COMET-3	NCT03862911	Mixed	1–3	Per physician discretion	RT	OS
LONESTAR	NCT03391869	NSCLC	1–3 (subset)	Ipilimumab/ nivolumab	RT	OS
HALT	NCT03256981	Oligoprogressive NSCLC with driver mutation	1–3	TKI	RT	PFS

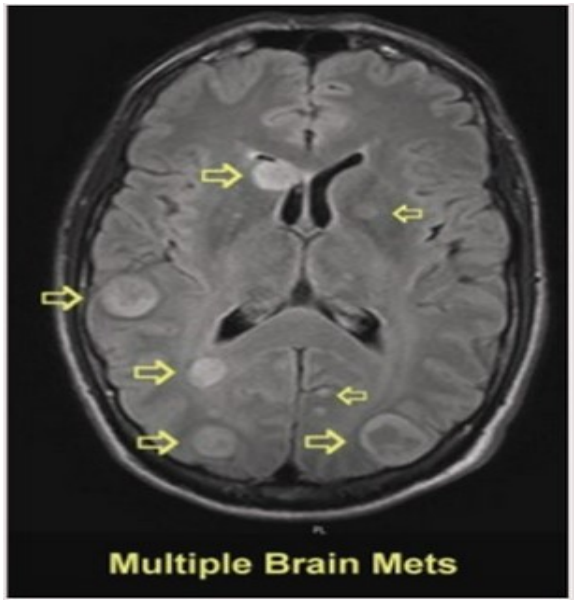
SMALL CELL LUNG CANCER: ANY UPDATE?







Brain failure in SCLC: one of the biggest challenges

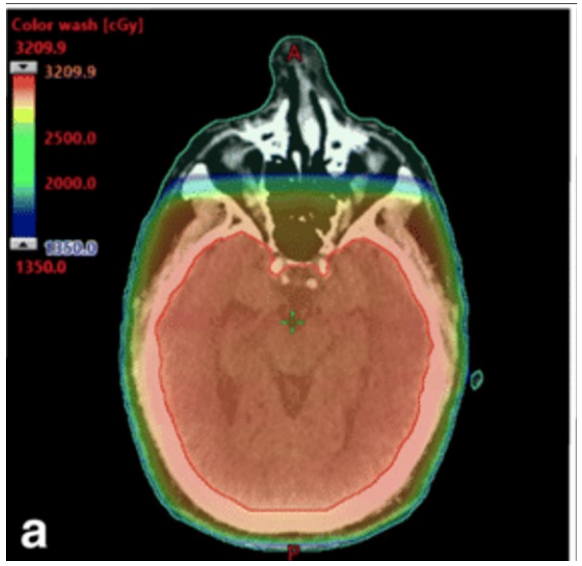


PCIO Meta-analysis

- 7 trials (987 patients with SCLC in CR)
  - No PCI (461 pts)
  - PCI (526 pts): Doses 8 Gy/1 fr to 40 Gy/20 fr

- Decrease of cumulative incidence of BM
  58.6% versus 33.3% in the PCI group (p<0.001)
- Improved 3-year disease free survival rate
  13.5% versus 22.3% in the PCI group (p<0.001)
- Improved 3-year overall survival rate (5.4% increase)
  15.3% versus 20.7% in the PCI group (p=0.01)

Auperin et al, NEJM 1999;341:476



- Traditonal WBRT includes in field the hippocampus
- Hippocampus is integral to learning and memory

Randomized Phase III Trial of Prophylactic Cranial Irradiation With or Without Hippocampal Avoidance for Small-Cell Lung Cancer (PREMER): A GICOR-GOECP-SEOR Study

Target population

- Adult with histologic or cytologic proof of SCLC (limited disease or extensive without brain metastases) candidate for PCI after response to chemotherapy or chemoradiation.
- Age ≥18 years.
- Karnofsky Index ≥ 80%.
- Negative brain MRI within one month of enrollment.

Exclusion criteria

- Prior radiotherapy to the brain
- Brain metastases or primary brain tumors.
- Evidence of progressive extracranial metastatic disease.
- Previous malignancy < 5 years ago except for adequately treated basal cell carcinoma of the skin and carcinoma in situ of the cervix.
- Any systemic anticancer treatment during PCI or within 3 weeks before start PCI.
- Pregnant women or women of childbearing potential who are sexually active and not willing or able to use medically acceptable forms of contraception.

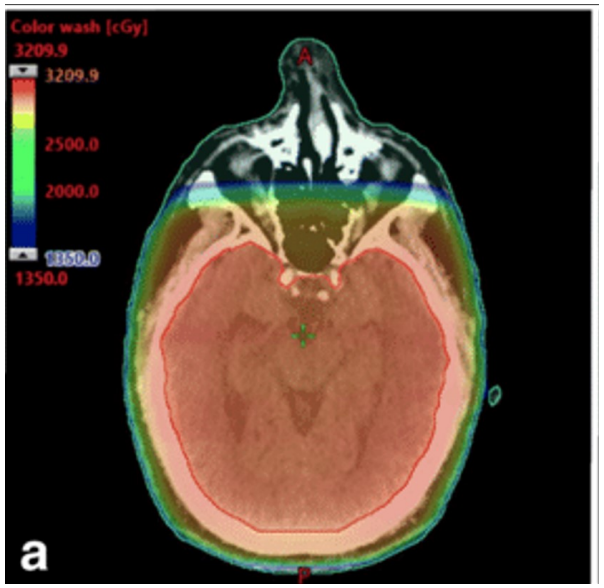
BASELINE ASSESSMENTS
Signed informed consent
Brain MRI
FCSRT-A
QLQ C30, BN20
CTCAE v4.0

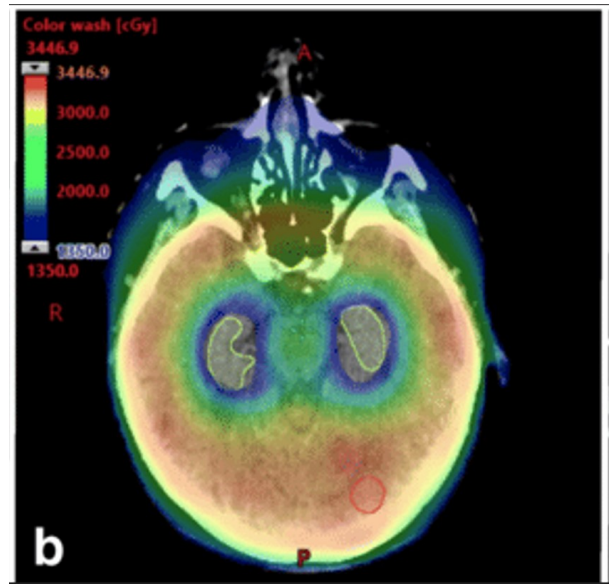
Randomization

PCI (25 Gy, 10 fractions)

PCI-HA (25 Gy, 10 fractions)

ASSESSMENTS AFTER PCI			
3 months	6 months	12 months	24 months
Brain MRI		Brain MRI	Brain MRI
FCSRT-A	FCSRT-B	FCSRT-A	FCSRT-B
QLQ C30, BN20	QLQ C30, BN20	QLQ C30, BN20	QLQ C30, BN20
CTCAE v4.0	CTCAE v4.0	CTCAE v4.0	CTCAE v4.0





Randomized Phase III Trial of Prophylactic Cranial Irradiation With or Without Hippocampal Avoidance for Small-Cell Lung Cancer (PREMER): A GICOR-GOECP-SEOR Study

CONCLUSION

Sparing the hippocampus during PCI better preserves cognitive function in patients with SCLC. No differences were observed with regard to brain failure, OS, and QoL compared with standard PCI.

Relevance

This study is an important step introducing a new therapeutic approach to patients with SCLC candidates for PCI. On the basis of the results of this study, we conclude that hippocampal avoidance-PCI should be considered standard of care for patients with SCLC who plan to receive PCI.

Conclusioni

- ✓Il trattamento radioterapico stereotassico risulta sicuro ed efficace sia nel trattamento del tumore primitivo che delle metastasi.

- ✓Lo sviluppo tecnologico ci consente di trattare sempre più pazienti con dosi radicali e a scopo curativo.

- ✓Il trattamento delle oligometastasi può migliorare l'outcome? Necessaria conferma dei dati ad oggi a disposizione tramite studi di fase III randomizzati.

- ✓Fondamentale la gestione multidisciplinare dei pazienti.

FIGHTING CANCER IS A TEAM EFFORT

Thank you