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De plaats van radiotherapie en de resultaten bij oligoprogressie

Charlotte Billiet, MD PhD

Radiotherapie-oncologie

Iridium Netwerk

Universiteit Antwerpen

Overview

- Oligometastatic disease
- RT for oligometastases
- RT for oligoprogression

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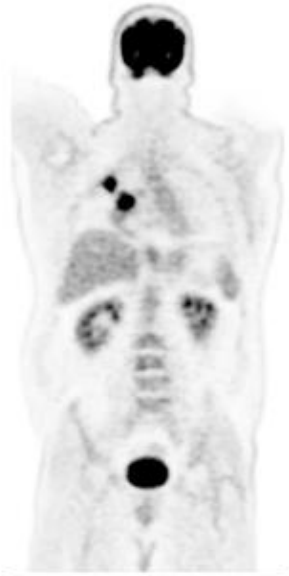
Oligometastatic disease

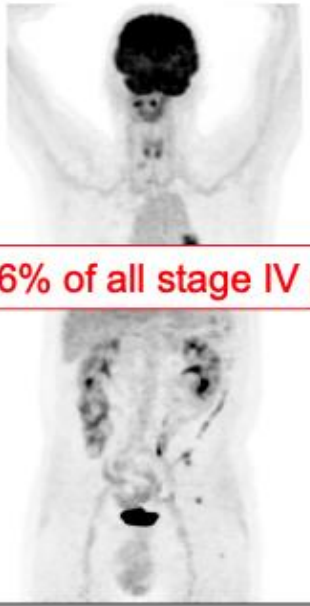
Hellman & Weichselbaum 1995

'Metastases are concentrated to a single or a limited number of organs.

… Some patient should be amenable to a curative therapeutic strategy.'

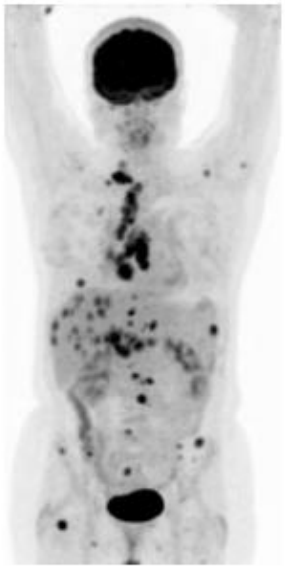


Locoregional



15-26% of all stage IV patients

Oligometastatic



Polymetastatic

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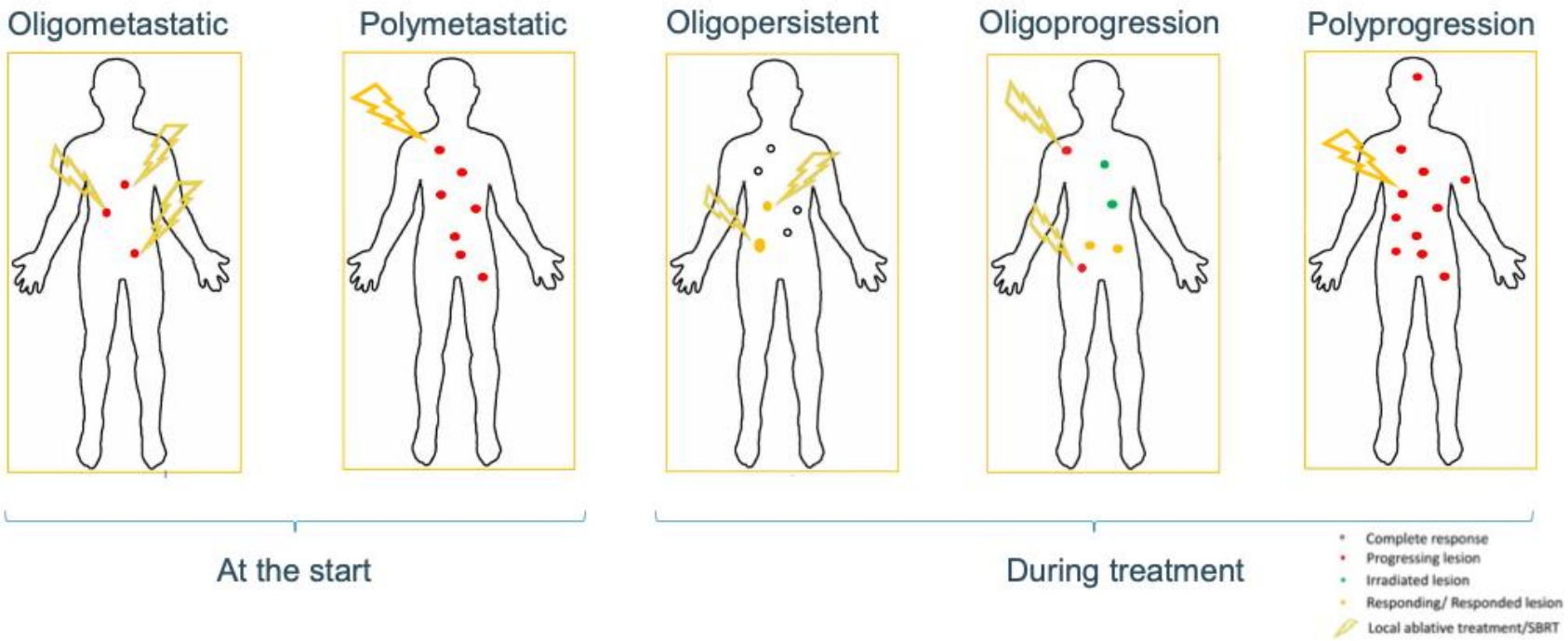
Hellman and Weichselbaum JCO 1995; Parish et al. IJRBOP 2014

Oligometastatic disease

Complex landscape



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Patel et al. Clin Oncol 2019

Oligometastatic disease

- Recent ESTRO and EORTC consensus recommendation
- 5 questions

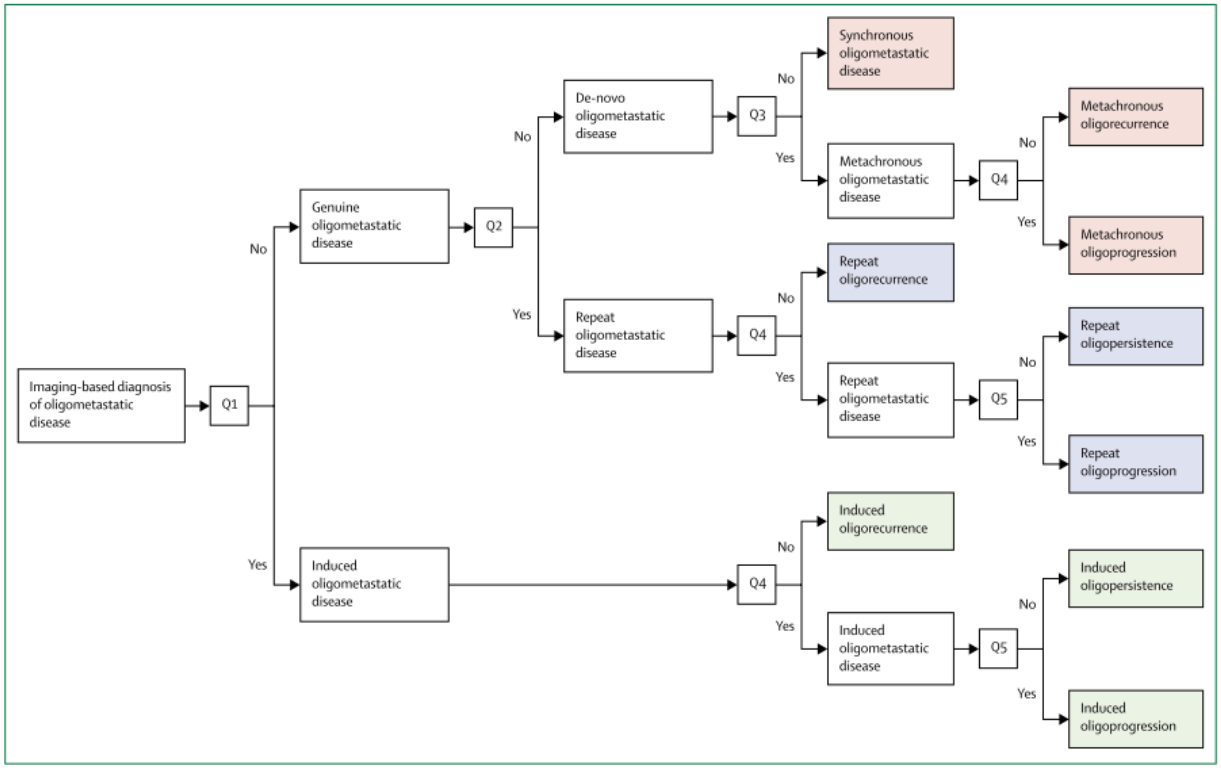

Figure 3: **Decision tree for classification of oligometastatic disease**
The decision tree starts with oligometastatic disease as umbrella term. Questions 1 and 2 differentiate between the upper-level oligometastatic states of de-novo (red), repeat (blue) and induced oligometastatic disease (green). Question 3 differentiates de-novo oligometastatic disease into synchronous and metachronous oligometastatic disease. Questions 4 and 5 subclassify into oligorecurrence, oligoprogression, and oligopersistence. Q1: Does the patient have a history of polymetastatic disease before current diagnosis of oligometastatic disease? Q2: Does the patient have a history of oligometastatic disease before current diagnosis of oligometastatic disease? Q3: Has oligometastatic disease been first diagnosed more than 6 months after the primary cancer diagnosis? Q4: Is the patient under active systemic therapy at the time of oligometastatic disease diagnosis? Q5: Are any oligometastatic lesions progressive on current imaging?

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Guckenberger et al. Lancet Oncol 2020

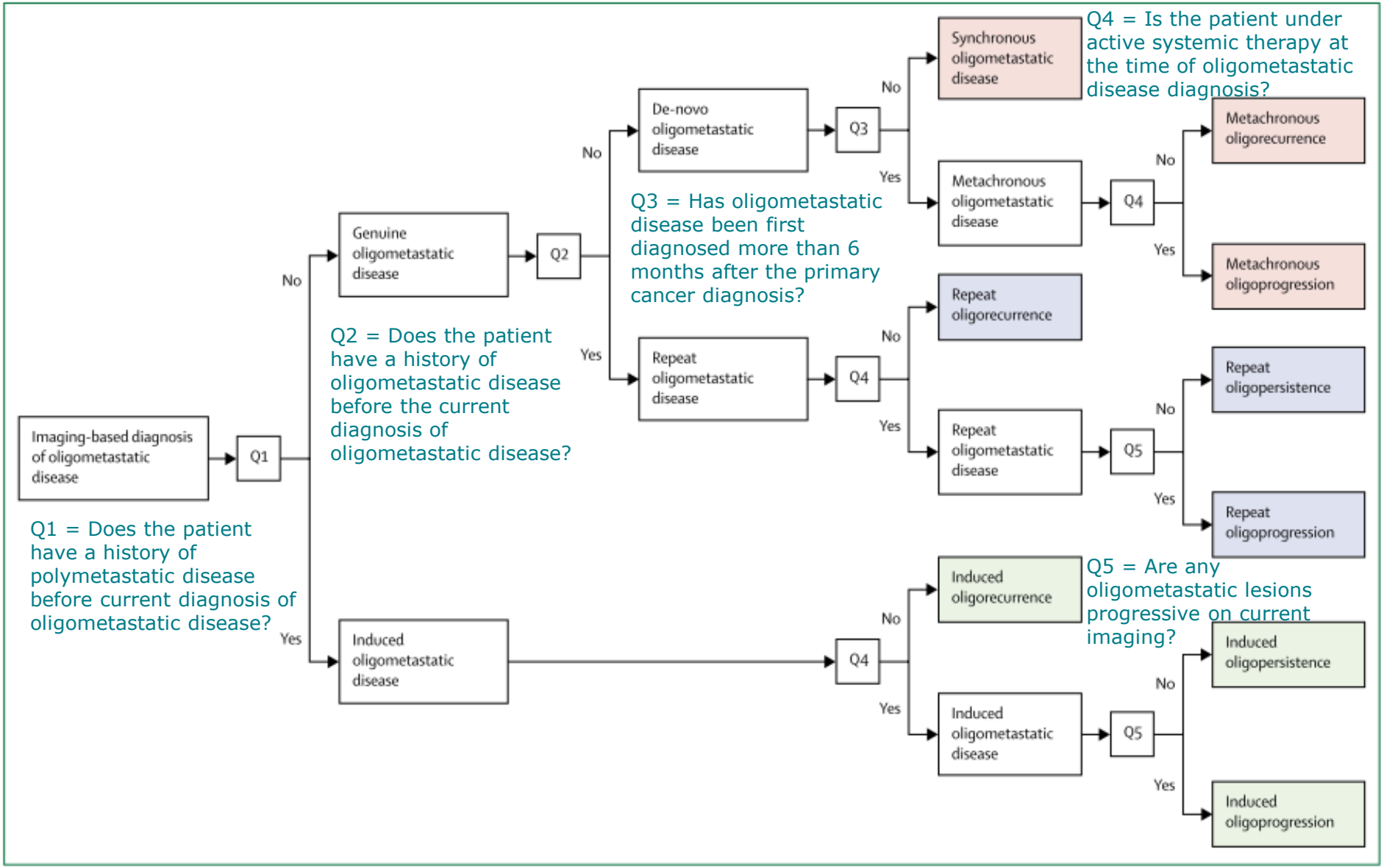

***Figure 3*: Decision tree for classification of oligometastatic disease**

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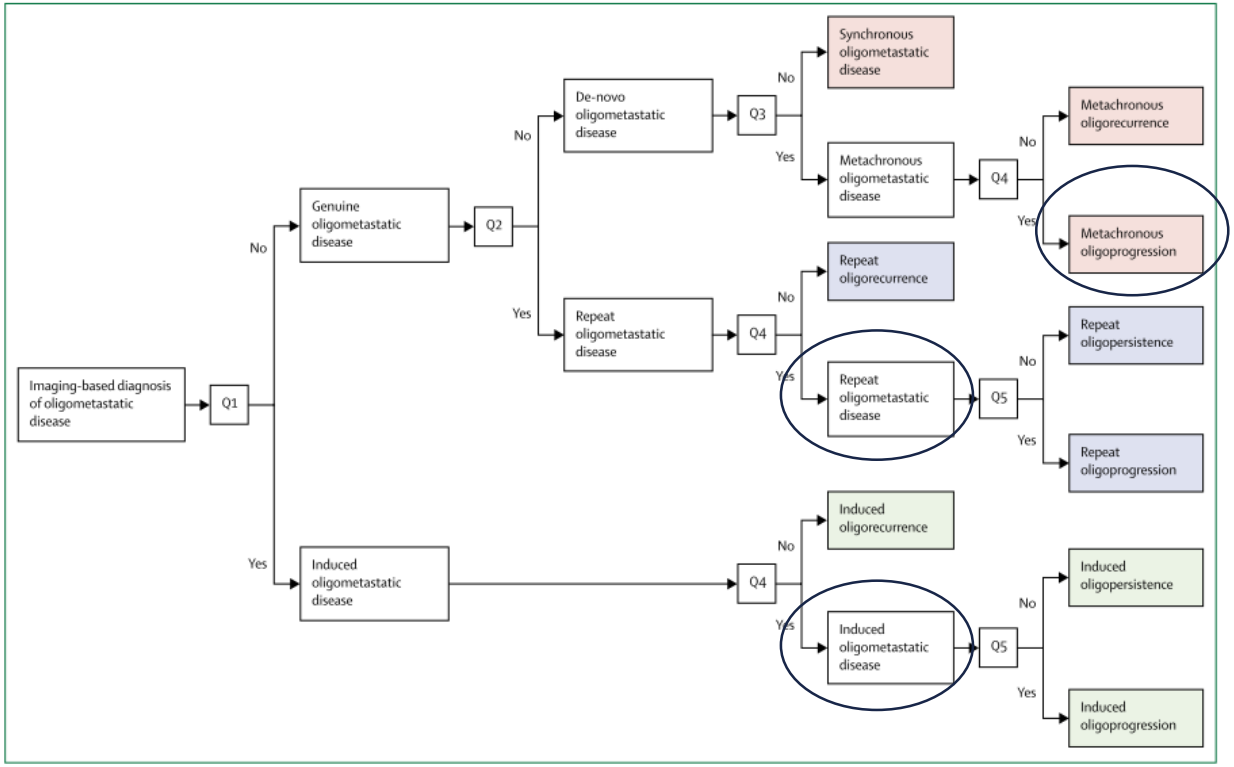
Oligometastatic disease

- Recent ESTRO and EORTC consensus recommendation



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Guckenberger et al. Lancet Oncol 2020

Oligometastatic disease

- System for classification of oligometastatic disease
- Important for local treatment (in and outside clinical trials)
- Dynamic model
- Prognostic value is currently tested

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Oligometastatic disease

- Current treatment guidelines for local therapy:

ESMO

Treatment of oligometastatic disease

•Stage IV patients with one to three synchronous metastases at diagnosis may experience long-term DFS following systemic therapy and local consolidative therapy (high-dose RT or surgery) [III, B]. Because of the limited evidence, these patients should be discussed within a multidisciplinary tumour board [II, B], and inclusion in clinical trials is preferred
•Although operative risk is low and long-term survival may be achieved, current evidence for surgery in oligometastatic disease is limited, and the relative contribution of surgery versus RT as local treatment modality has not been established yet
•Stage IV patients with limited metachronous metastases may be treated with a radical local therapy (high-dose RT or surgery) and may experience longterm DFS [IV, B]. However, this is based mainly on retrospective data and inclusion in clinical trials is preferred
•Stage IV patients with driver mutations, with oligoprogression while on molecular-targeted therapy, may be treated with a radical local treatment (high-dose RT or surgery) and may experience long-term DFS [IV, C]. However, this is based mainly on retrospective data and inclusion in clinical trials is preferred
•Solitary lesions in the contralateral lung should, in most cases, be considered as synchronous secondary primary tumours and, if possible, treated with curative-intent therapy [IV, B]

Which patients?
1- 3 Synchronous M+
Limited metachronous
Oligoprogression

high-dose RT or surgery

Endpoint: DFS

Limited evidence

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Planchard et al. Annals Oncol 2019

Oligometastatic disease

- Current treatment guidelines for local therapy:

NCCN

- Definitive RT to oligometastases (limited number is not universally defined but clinical trials have included up to 3–5 metastases), particularly SABR, is an appropriate option in such cases if it can be delivered safely to the involved sites.
  In two randomized phase II trials, significantly improved progression-free survival was found for local consolidative therapy (RT or surgery) to oligometastatic lesions versus maintenance systemic therapy or observation for patients not progressing on systemic therapy.

- In the setting of progression at a limited number of sites on a given line of systemic therapy (oligoprogression), local ablative therapy to the oligoprogressive sites may extend the duration of benefit of the current line of systemic therapy.

- When treating oligometastatic/oligoprogressive lesions, if SABR is not feasible, other dose-intensive accelerated/hypofractionated conformal radiation therapy regimens may be used.

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NCCN guidelines 2020

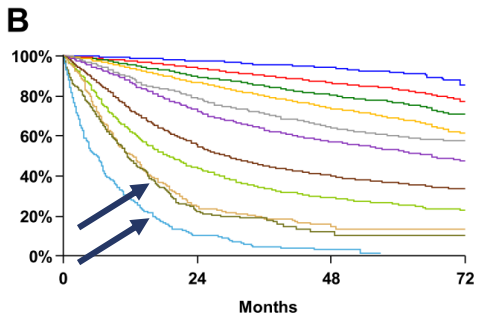
Oligometastatic disease

- 8th TNM classification

M: Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis present
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion[d]
M1b	**Single extrathoracic metastasis[e]**
M1c	**Multiple extrathoracic metastases in one or more organs**

Solitary extrathoracic metastasis (M1b= stage IVA)

-> improved survival compared to multiple extrathoracic metastases (M1c= stage IVB)



Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

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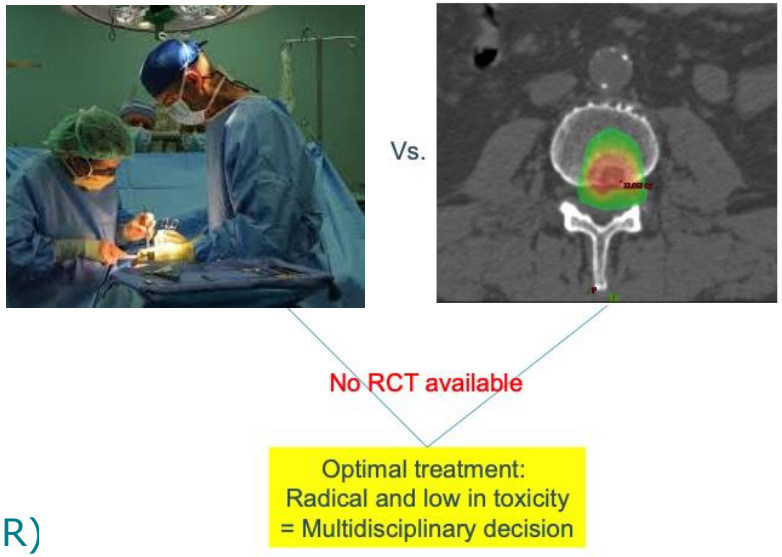
Oligometastatic disease

Metastasis directed therapy (MDT):

- **Surgery**
  - Pathology
  - R0 resection (palliation vs diagnosis)
- **Radiotherapy**
  - Less invasive
  - Curative dose (vs palliative dose)
  - Stereotactic ablative body radiotherapy (SABR)
- **Radiofrequentie ablatie (RFA)**
- …



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Oligometastatic disease

- Evidence for surgery:

Study	n	Performance Status (ECOG)	Location of Oligometastatic Disease	Survival
Raz et al., 2011	20	0–1	100%, adrenal	34%, 5-y
Mercier et al., 2005	23	NR	100%, adrenal	23%, 5-y
Collaud et al., 2012	29	NR	66%, brain 27%, intrapulmonary 7%, adrenal	36%, 5-y
Gray et al., 2014	38	NR	100%, brain	29%, 5-y
Daniels and Wright, 2005	15	NR	100%, brain	60%, 5-y
Bae et al., 2015	86	NR	100%, brain	15%, 5-y
Yuksel et al., 2014	28	NR	100%, brain	8%, 5-y
Hanagiri et al., 2012	17	0-1	11%, brain 11%, adrenal	25.1%, 5-y
Congedo et al., 2012	53	0–1	71%, brain 15%, adrenal 14%, other	24%, 5-y
De Ruysscher, 2012	39	0–2	44%, brain 10%, adrenal	18%, 3-y
Khan et al., 2006	23	0–1	61%, brain 9%, adrenal 30%, other	20-mo median follow-up
Endo et al., 2014	34	0–1	50%, brain 12%, adrenal	47%, 5-y
Yamaguchi et al., 2016	23	0–1	57%, brain 9%, adrenal	42%, 5-y
Griffioen et al., 2013	61	0–2	59%, brain 6%, adrenal	38%, 2-y

-Mostly adrenal and brain
-Highly selected patients
-Good 5y OS results

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Oligometastatic disease

- Evidence for radiotherapy:
- Several recent large randomized trials:
  - Gomez et al 2019
  - Palma et al 2019 (SABR-COMET)
  - De Ruysscher et al 2012 (update 2019)
  - Yvengar et al 2014

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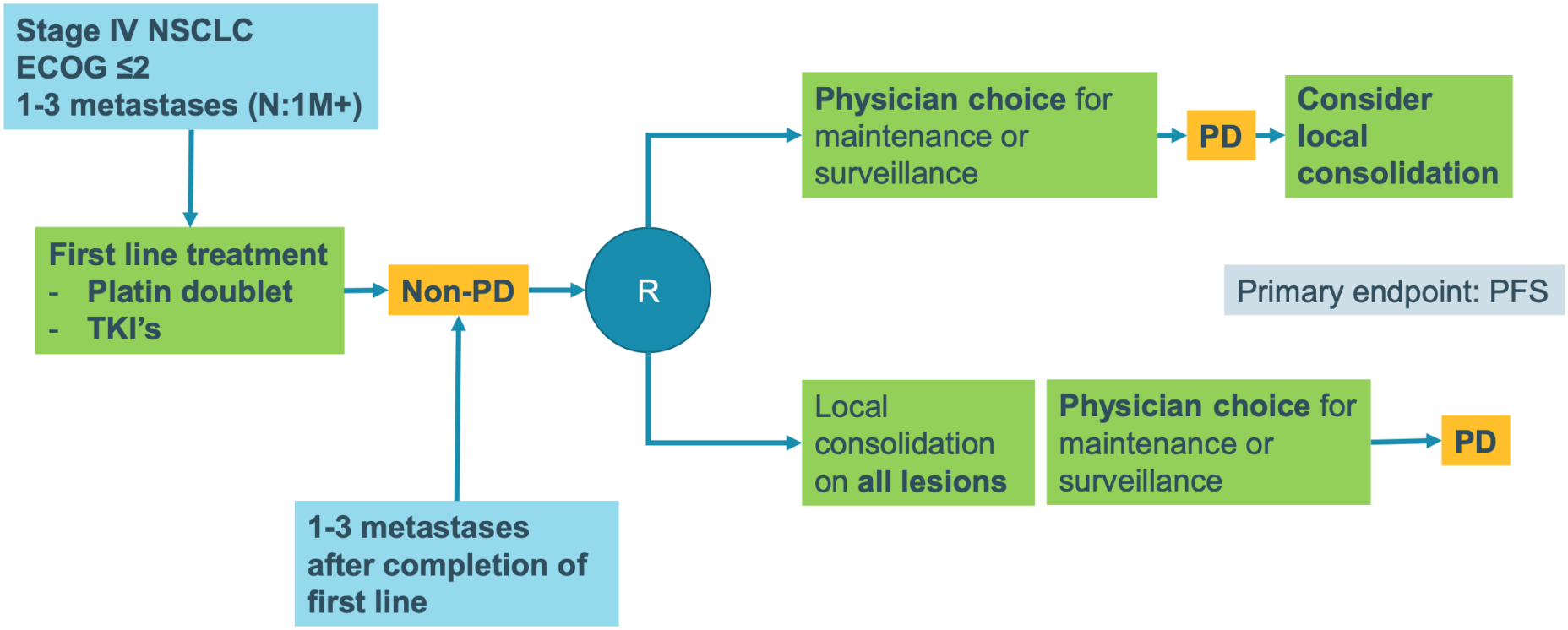
RT for oligometastases

- Gomez et al 2019 - multicenter, randomized, phase II trial



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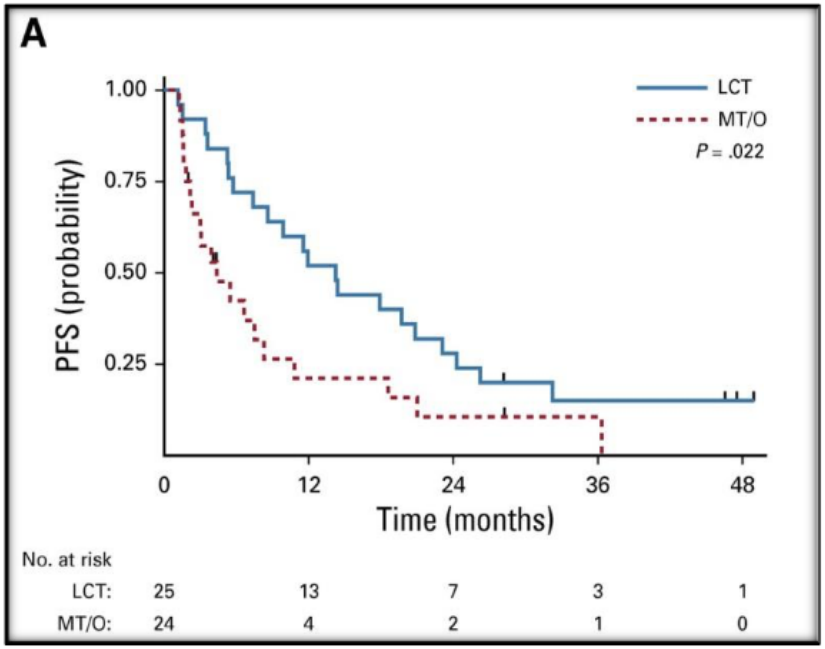
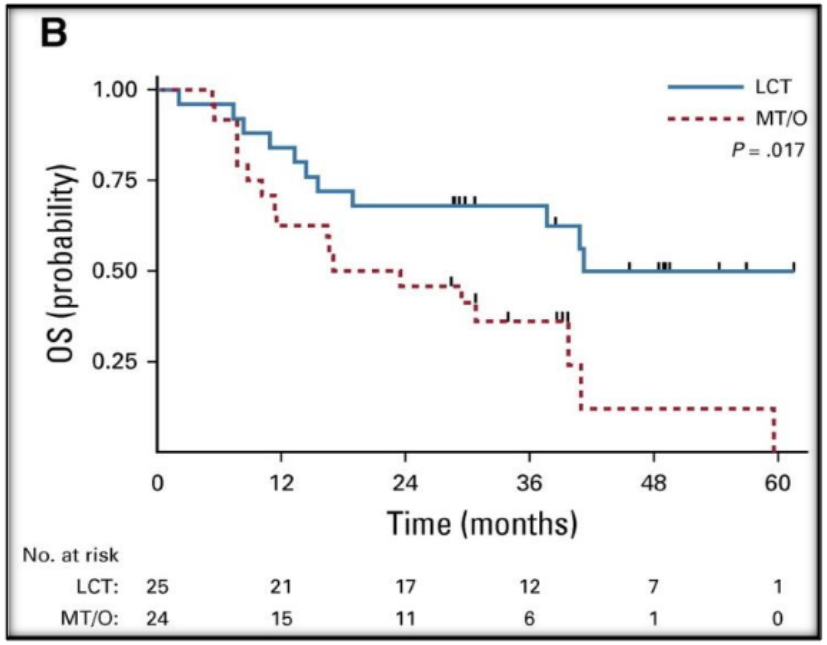
Gomez et al. J Clin Oncol 2019

RT for oligometastases

mPFS 14.4 vs 4,4 in favour of LAT



mOS 41.2 vs 17.0 in favour of LAT



- Early trial closure because of a significant PFS benefit
- Clear PFS and OS benefit
- No additional >= grade 3 AE in either arms
- Mostly synchronous M+

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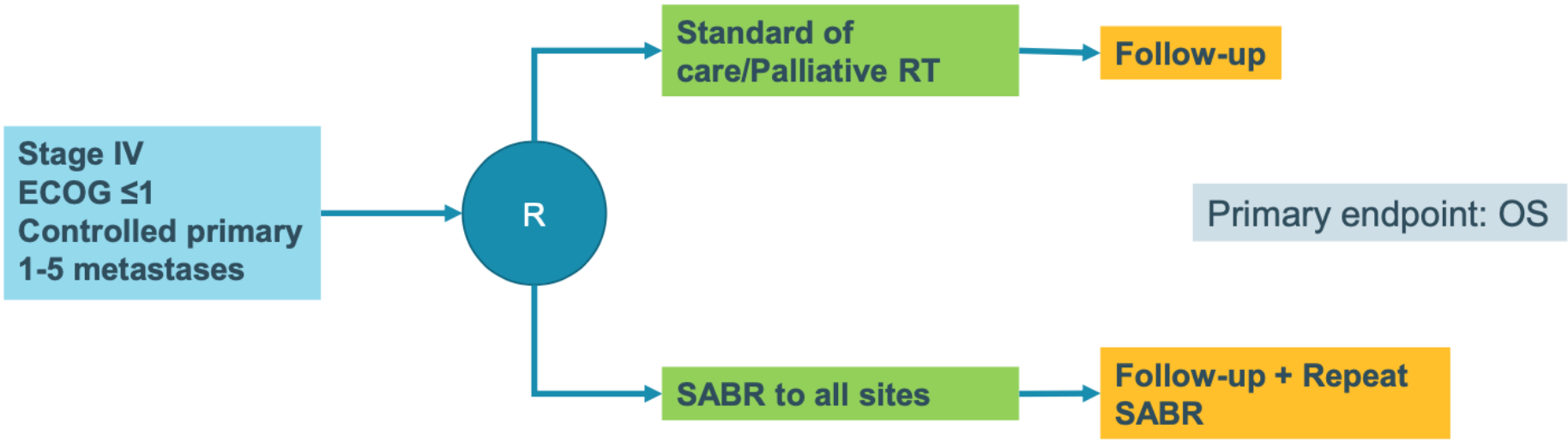
RT for oligometastases

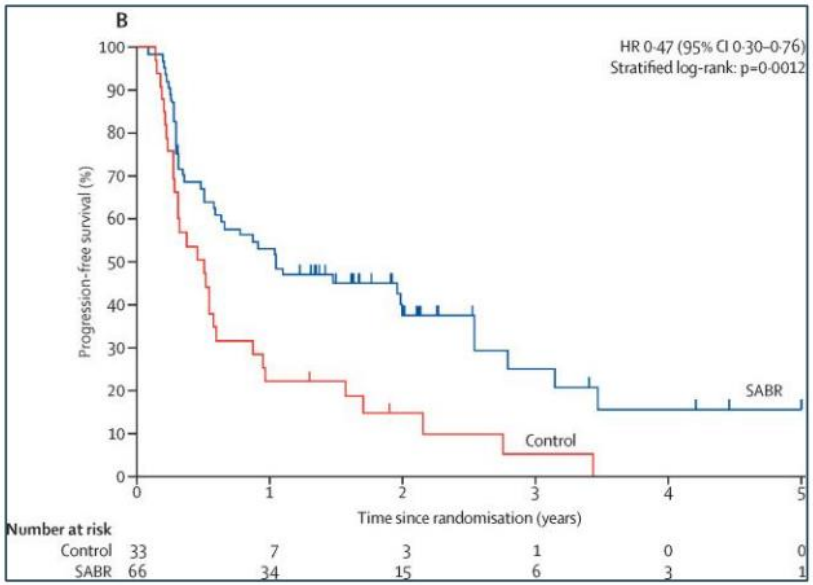
- SABR COMET (Palma et al 2019) - multicenter, randomized, phase II trial



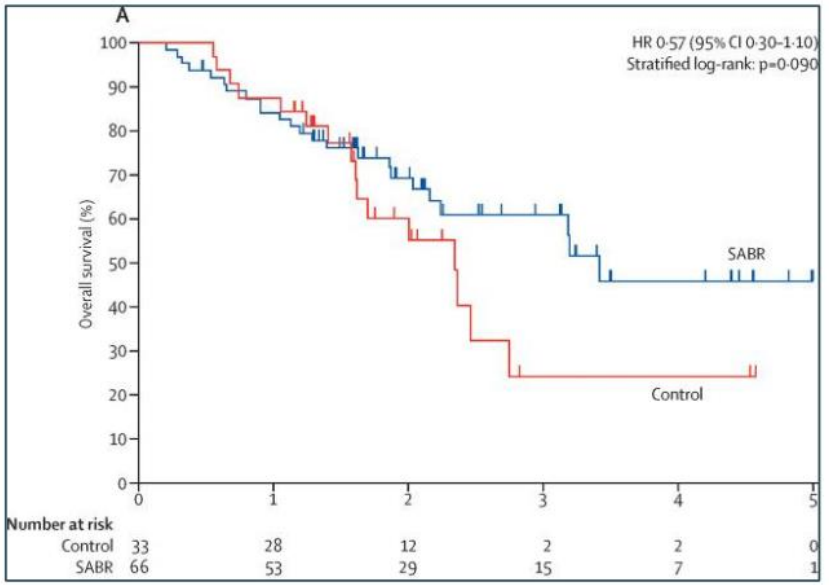
Palma et al. Lancet 2019

RT for oligometastases

mPFS 12m vs 6m in favour of SABR



mOS 41m vs 28m in favour of SABR



- 29% vs 9% grade II or higher AE in SABR arm
- 4.5% of treatment related deaths in SABR arm
- Primary endpoint: OS

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Palma et al. Lancet 2019

RT for oligometastases

Conclusions:

- Most trials involving **synchrone oligoM+**
- Recent randomized trials demonstrate **PFS and OS benefit**
- LAT = Radical RT (SABR) or surgery
- Uncertainties
  - Timing: controversial
  - Maximum number of M+?

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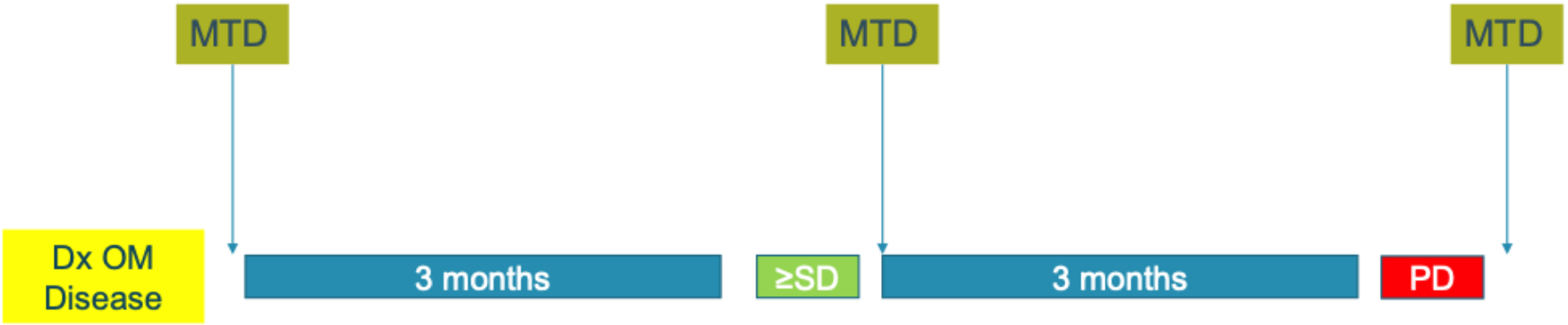
Timing

- When to treat oligometastatic disease?



+ Full treatment upfront
+ Better performance status
- Overtreatment
- Patient selection

+ Patient selection
+ Minimal burden
- Weakened pt
- Overtreatment?

+ Patient selection
- Only oligoprogression
- Too late?

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Number of M+

J Thorac Oncol. 2019 Dec;14(12):2109-2119. doi: 10.1016/j.jtho.2019.07.025. Epub 2019 Aug 6.

Definition of Synchronous Oligometastatic Non-Small Cell Lung Cancer-A Consensus Report

Anne-Marie C Dingemans [1], Lizza E L Hendriks [2], Thierry Berghmans [3], Antonin Levy [4], Baktiar Hasan [5], Corinne Faivre-Finn [6], Matteo Giaj-Levra [7], Niccolò Giaj-Levra [8], Nicolas Girard [9], Laurent Greillier [10], Sylvie Lantuéjoul [11], John Edwards [12], Mary O'Brien [13], Martin Reck [14], Egbert F Smit [15], Paul Van Schil [16], Pieter E Postmus [17], Sara Ramella [18], Yolande Lievens [19], Mina Gaga [20], Nir Peled [21], Giorgio V Scagliotti [22], Suresh Senan [23], Luiz Paz-Ares [24], Matthias Guckenberger [25], Fiona McDonald [26], Simon Ekman [27], Tanja Cufer [28], Hester Gietema [29], Maurizio Infante [30], Rafal Dziadziuszko [31], Solange Peters [32], Ramon Rami Porta [33], Johan Vansteenkiste [34], Christophe Dooms [34], Dirk de Ruysscher [35], Benjamin Besse [36], Silvia Novello [22]

- Disagreement of expert opinions:

-lack of data on the maximum number that should be included in a definition.

- lack of prospective data defining the maximum number of metastasis / organs that can be technically treated with radical intent and result in improved outcome

-Survey: maximum of 3 up to 5 M+

-Consensus statement: a large number of metastasis (i.e. > 5) can technically be treated radically, this is not in line with the term oligo and therefore we do not consider this oligometastatic disease.

a maximum of 5 metastases and 3 organs is proposed. Mediastinal lymph node involvement is not counted as a metastatic site

Currently ongoing: SABR COMET for 4-10 M+

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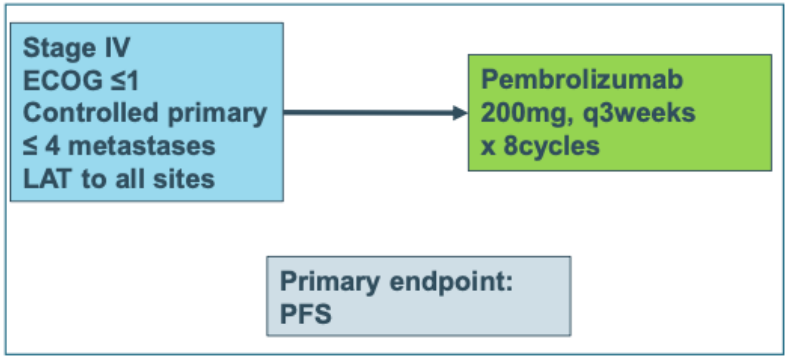
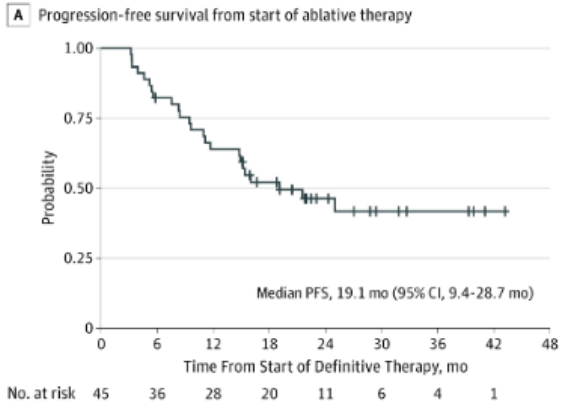
Dingemans et al. J Thorac Oncol 2019

Immunotherapy

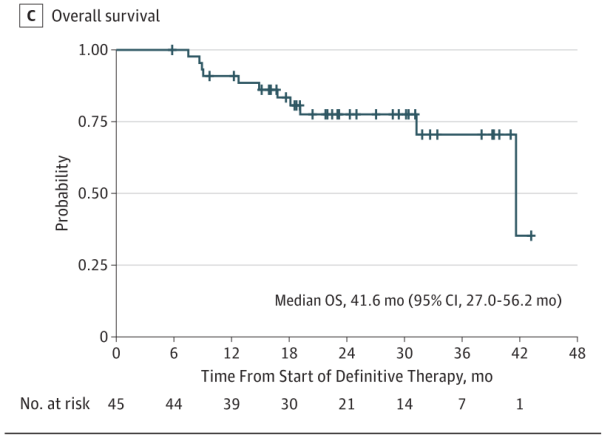
- Quid in the era of IO?





- Single-arm phase II trial
- All NSCLC
- Pembrolizumab after LAT for oligometastatic NSCLC appears to improve PFS with no reduction in QoL

No reduction in QOL



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Bauml et al. JAMA 2019

Immunotherapy

- However: toxicity!

Trial	Patient Characteristics	Radiotherapy	Immunotherapy	Sequencing	Toxicity
Tian et al. WCLC 2019 Retrospective	Mixed Tumour Types Lung lesions (86% 1 lesion) No active BM 36% Prior Lung RT (40% RT 'overlapping')	Dose #?	68% IO 14% IO/IO 18% IO/Chemo	25% 'Interdigitated' 42% Pre & post RT 32% Pre or post RT	Pneumonitis ≥G3 11% Any G 38% Inter vs 21% Not 29% IO vs 63% IO/IO ≥G3 1 lobe 8% 2 lobes 67%
Siva et al. Prospective single arm	Metastases PS 0-1	30Gy/1-10#	Pembrolizumab 8 cycles	IO after SBRT	Pneumonitis ≥G3 15% G4/5 0%
Leal et al. Prospective single arm	PS 0-1 NSCLC oligometastatic	30-50Gy in 5#	Durvalumab & Tremelimumab 4 cycles then Maintenance Durvalumab	IO after SBRT	All Toxicity ≥G3:25%

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RT for oligoprogression

- Patients with stage IV disease on an active systemic therapy
- Possible in different stages of disease

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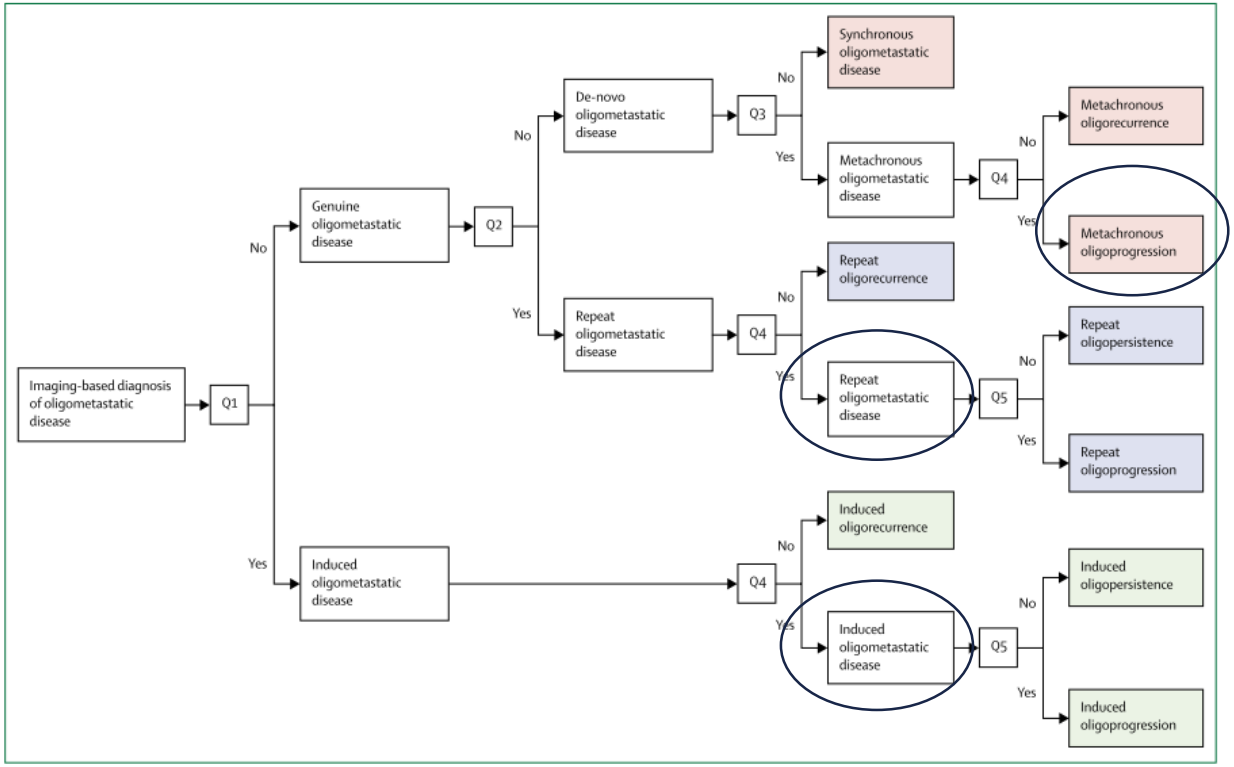
RT for oligoprogression

- Recent ESTRO and EORTC consensus recommendation



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Guckenberger et al. Lancet Oncol 2020

RT for oligoprogression

- Best described in patients with NSCLC with driver mutations treated with molecular targeted therapy.
  - Resistance develops with a median PFS of 10 to 14 months.
  - Oligoprogressive sites may occur as oligo-clones that became resistant
  - LAT for these oligoprogressive sites can prolong disease control prior to widespread of dissemination of the resistant clones
  - Continuation of TKI beyond RECIST progression is advised as TKI-sensitive clones may regrow and result in rapid PD with the potential risk of flare-up of symptoms.

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RT for oligoprogression

- Limited evidence, most small retrospective trials
- Outcomes are highly variable
- Probably subset of NSCLC patients with oligometastatic disease who appear to benefit

TABLE 3. Studies of Local Ablative Therapy for Extra- and Intra-cranial Oligoprogressive NSCLC after Molecular Targeted Therapy

Author (Publication year)	Study population	Definition of oligoprogressive disease	Site of metastatic disease	Study design	No. of patients	Types of LAT	Treatment outcomes after LAT	
							Median PFS2 (mo)*	Median OS (mo)
Weickhardt et al. (2012)[19]	*EGFR* mutant or *ALK* rearranged NSCLC with resistance to erlotinib or crizotinib	4 sites or fewer progression	Extracranial	Retrospective	15	Surgery, RT	4.0	NR
Yu et al. (2013)[69]	*EGFR* mutant NSCLC with resistance to erlotinib or gefitinib	Less than 5 sites of disease at the time of LAT**	Extracranial	Retrospective	18	Surgery, RT, RFA	10.0	41.0
Gan et al. (2014)[70]	*ALK* rearranged NSCLC with resistance to crizotinib	4 sites or fewer progression	Extracranial	Retrospective	14	Surgery, RT	5.5	39.0
Shukuya et al. (2011)[74]	*EGFR* mutant NSCLC with resistance to gefitinib	Isolated CNS progression	Intracranial	Retrospective	17	SRS, WBRT	2.7 (overall) 5.7 (extracranial)	13.4
Weickhardt et al. (2012)[19]	*EGFR* mutant or *ALK* rearranged NSCLC with resistance to erlotinib or crizotinib	Isolated CNS progression	Intracranial	Retrospective	10	SRS, WBRT	7.1	NR
Takeda et al. (2013)[68]	*ALK* rearranged NSCLC with resistance to crizotinib	Isolated CNS progression	Intracranial	Retrospective	7	SRS, WBRT	5.5	NR

RT for oligoprogression

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Gan et al. (2014)[70]	*ALK* rearranged NSCLC with resistance to crizotinib	4 sites or fewer progression	Extracranial	Retrospective	14	Surgery, RT	5.5	39.0
Shukuya et al. (2011)[74]	*EGFR* mutant NSCLC with resistance to gefitinib	Isolated CNS progression	Intracranial	Retrospective	17	SRS, WBRT	2.7 (overall) 5.7 (extracranial)	13.4
Weickhardt et al. (2012)[19]	*EGFR* mutant or *ALK* rearranged NSCLC with resistance to erlotinib or crizotinib	Isolated CNS progression	Intracranial	Retrospective	10	SRS, WBRT	7.1	NR
Takeda et al. (2013)[68]	*ALK* rearranged NSCLC with resistance to crizotinib	Isolated CNS progression	Intracranial	Retrospective	7	SRS, WBRT	5.5	NR

Intracranial oligoprogression

- Poor blood-brain barriere penetration of targeted agents
- Predilection of EFGR/ALK+ NSCLC for CNS
  - Trial: 19% cumulative CNS M+ at 2y (for EGFR+)
  - Trial: 20-46% CNS M+ at time of PD (for ALK)
- Continuation of targeted R/ after LAT seems beneficial

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RT for oligoprogression

- Retrospective trial 2019:
  - 206 EGFR mutated NSCLC patients
  - Oligoprogression <= 5 sites
  - Local ablative therapy (RT or surgery) with continuing TKI (first-line therapy)
- Results:
  - 2-year OS: 78.9%
  - median OS : 37.0 months
  - median PFS after LT 18.0 months (up to off-TKI)

First-line continual EGFR-TKI plus local ablative therapy demonstrated survival benefit in EGFR-mutant NSCLC patients with oligoprogressive disease

Qinghua Xu[1,2,*], Hui Liu[2,*], Shuyan Meng[3,*], Tao Jiang[3,*], Xuefei Li[4], Shixiong Liang[2], Shengxiang Ren[3], Caicun Zhou[3,5,✉]

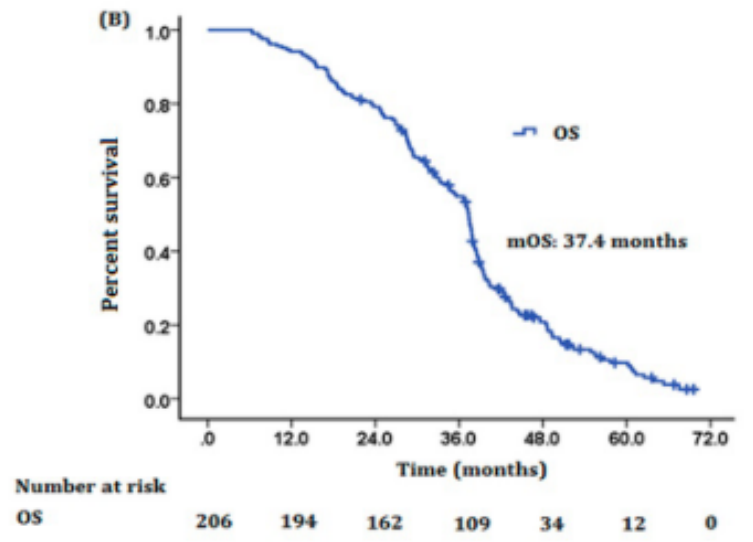

Figure 1. Kaplan-Meier plot of (A) PFS1, PFS2 and (B) OS for all patients in this study cohort. Abbreviations: mPFS, media progression-free survival; mOS, media overal survival.

Xu et al. Journal of cancer 2019

RT for oligoprogression

- Retrospective trial 2017:
  - 46 EGFR mutated NSCLC patients
  - Oligoprogression <= 5 sites
  - Local ablative therapy with continuing TKI
- Results:
  - 2-year OS: 65.2%
  - median PFS after LAT 7.0 months
  - Prognostic factors for OS in multivariate analysis:
    - EGFR mutation (exon 19 vs. exon 21)
    - Sites of local therapy (brain vs. lung or bone)
    - Time from first PD to local therapy (<6m vs. >6m)

Local Therapy for Oligoprogressive Disease in Patients With Advanced Stage Non–small-cell Lung Cancer Harboring Epidermal Growth Factor Receptor Mutation

Bo Qiu,[1,3] Ying Liang,[1,4] QiWen Li,[1,3] GuiHong Liu,[2] Fang Wang,[1,5] ZhaoLin Chen,[1,3] MengZhong Liu,[1,3] Ming Zhao,[1,6] Hui Liu[1,3]

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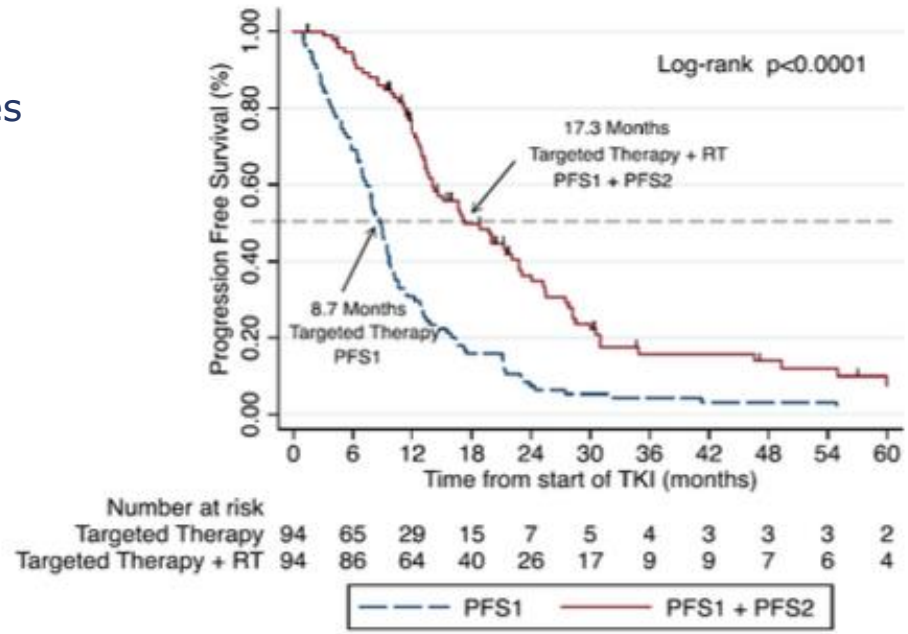
Qiu B. et al. Clin Lung Cancer 2017

RT for oligoprogression

- Abstract ASTRO 2019:
  - 81 NSCLC patients
  - Targetable mutation
  - Oligoprogression <= 5 sites
  - **Randomized**: +/- LAT
  - Results: + **8.6m PFS**



Holt et al. ASTRO 2019

RT for oligoprogression

Conclusions:

- LAT seems effective for patients with oligoprogression
- Overall limited evidence
  - Most trials with targeted therapies
  - Also possible for non-driver mutated NSCLC
  - LAT for oligoprogression included in international guidelines (NCCN, ESMO)
- Uncertainties
  - Criteria for patient selection -> Important to investigate which subgroups of patients with benefit
  - Timing

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Timing

- Immediately LAT in case of oligoPD (symptomatic and asymptomatic)?

-> Symptomatic oligoPD worse PFS (marginally significant)

Table 2. Univariable analysis of clinical factors potentially associated with PFS and OS.

Characteristic	mPFS1 (m)	HR (95%CI)	*p* Value	mPFS2 (m)	HR (95%CI)	*p* Value	mOS (m)	HR (95%CI)	*p* Value
Age (year)									
<65	10.8	1.25	0.148	18.6	1.26	0.092	37.6	1.29	0.131
≥65	10.5	**(0.92-1.68)**		17.4	**(1.01-1.63)**		37.1	**(0.96-1.74)**	
Gender									
Male	9.8	0.59	<0.001	16.9	0.55	<0.001	34.2	0.47	<0.001
Female	11.3	**(0.43-0.77)**		19.4	**(0.41-0.73)**		38.6	**(0.34-0.64)**	
ECOG performance status									
0~1	10.7	1.08	0.614	18.4	1.06	0.739	37.5	0.99	0.745
2	10.7	**(0.79-1.49)**		18.3	**(0.77-1.45)**		37.3	**(0.71-1.38)**	
Histology									
Adenocarcinoma	11.0	1.94	0.001	18.7	1.87	0.001	37.7	1.98	<0.001
Nonadenocarcinoma	7.9	**(1.32-2.84)**		13.6	**(1.27-2.74)**		25.2	**(1.36-2.89)**	
Disease stage									
IIIB	11.5	1.38	0.068	19.4	1.35	0.096	38.4	1.43	0.069
IV	10.5	**(0.97-1.96)**		18.2	**(0.95-1.91)**		37.2	**(0.97-2.10)**	
Smoking status									
Non-smoker	11.2	0.69	0.009	19.2	0.68	0.006	37.9	0.63	0.003
Present or former smoker	9.8	**(0.52-0.92)**		17.3	**(0.51-0.90)**		35.4	**(0.47-0.86)**	
Metastases number									
1	11.7	0.59	<0.001	19.8	0.62	0.001	39.5	0.56	<0.001
>1	9.9	**(0.44-0.79)**		16.7	**(0.47-0.83)**		33.4	**(0.41-76)**	
EGFR mutation									
Exon 19 deletion	13.3	4.93	<0.001	21.9	5.1	<0.001	41.6	5.4	<0.001
Exon 21 L858R	9.2	**(3.53-6.89)**		15.6	**(3.64-7.11)**		28.9	**(3.77-7.74)**	
Response to first-line EGFR TKIs									
Partial or complete response	11.5	0.34	<0.001	19.5	0.34	<0.001	38.5	0.35	<0.001
Stable disease or disease progression	7.4	**(0.25-0.46)**		13.1	**(0.25-0.46)**		23.8	**(0.25-0.48)**	
Oligoprogressive symptom									
Symptomatic	10.7	0.98	0.550	16.7	0.85	0.080	34.2	0.91	0.215
Asymptomatic	10.8	**(0.70-1.36)**		18.4	**(0.58-1.12)**		37.6	**(0.62-1.30)**	

Abbreviations: m, months; HR, hazard ratio; mPFS, media progression-free survival; mOS, media overal survival; ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

Abbreviations: m, months; HR, hazard ratio; mPFS, media progression-free survival; mOS, media overal survival; ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

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Timing

- Little data on the safety of combining SABR with targeted agents

Table 4
Major studies on RT and TKIs.

Author and year	Study type	N	Tumor site	RT technique/ dose/fractionation	Combination (concomit, other.)	G3-4 Non-HEM AEs	Treatment related deaths	Incomplete RT
(Iyengar et al., 2014)	Phase II	24	Oligometastatic NSCLC	SBRT 27-33 Gy/3 fx 35-40 Gy/ 5 fx	E 1 week before and during SBRT	28%	13%	0
(Wang et al., 2014)	Phase II	14	Advanced (pre-treated) NSCLC	SBRT 48-60 Gy/3 fx	G during SBRT and continued as maintenance	29% (G3) 0 (G4)	0	N.R.
(Herman et al., 2013)	Phase II	48	Resectable PA	IMRT 50.4 Gy/28 fx	CT-RT (CAP) + E	44%	N.R.	17%
(Valentini et al., 2008)	Phase I-II	41	LARC	3DCRT 50.4 Gy/28 fx	CT-RT (5-FU) + G	41%	0	12.8%
(Lee et al., 2014)	Phase II R	80	BM	3DCRT 20 Gy/5 fx	WBRT +/-E	rash: 5% vs 20% fatigue: 35% vs 17.5%	0	15% vs 15%
(Welsh et al., 2013)	Phase II	40	BM	3DCRT 35 Gy/14 fx	WBRT + E (u.p.)	rash: 15% fatigue: 12.5% diarrhoea: 10%	0	N.R.
(Zhuang et al., 2013)	Phase II R	54	BM	3DCRT 30 Gy/10 fx	WBRT +/- E	anorexia: 0 vs 8.6% (P < 0.05) dizziness: 3.2 % vs 4.3%	0	N.R.
(Pesce et al., 2012)	Phase II R	59	BM	3DCRT 30 Gy/10 fx	WBRT + TMZ (u.p.) vs WBRT + G (u.p.)	18.6% vs 37.5%	7% vs 6.2%	0
(Martins et al., 2013)	Phase II R	95	LA-SCCHN	IMRT 70 Gy/35 fx	CT-RT (CDDP) +/- E	rash: 2% vs 13% (P= .005) GI: 43% vs 48% (P= .43)	0 (both arms)	10% vs 6% (P=.31)
(Martinez et al., 2008)	Phase II R	90 (*)	LA-NSCLC	3DCRT 66Gy/33 fx	RT +/- E	37.9% vs 65% (P=0.016)	0 vs 1.6%	30% vs 60%
(Hammel et al., 2016)	Phase III R	133	Unresectable PA	3DCRT 54Gy/30 fx	Induction GEM alone vs GEM + E à CT vs CT-RT	nausea: 0 vs 5.9% (P= .008)	0	18% (CT-RT) group
(Arias de la Vega et al., 2012)	Phase I	13	LA-SCCHN	3DCRT 63Gy/35 fx	CT-RT (CDDP) + E	mucositis: 53% (all dose levels) skin toxicity: 23% (levels II/III) diarrhea: 15% (level III)	0	N.R
(Ahn et al., 2016)	Phase I	13	LA-SCCHN	IMRT 70 Gy/35 fx	Induction TPF-Eà CT-RT (CDDP+BEV)+E	GI bleeding/ perforation 15.5% diarrhea: 7.5%	0	15.3%
(Ramella et al., 2013)	Phase I-II	60	LA or metastaticNSCLC	3DCRT 59.4Gy/33 fx	Standard CT-RT +E	esophagitis: 2% pneumonitis: 8% rash: 7% diarrhea: 5%	3.3%	N.R.
(Chadha et al., 2016)	Phase I	17	Unresectable PA	3DCRT 50.4Gy/28 fx	CT-RT (CAP+BEV) + E	17.6% (level V)	0	0
(Jiang et al., 2014)	Phase I	18	Unresectable PA	3DCRT 50.4Gy/ 28 fx	CT-RT (CAP) + E	0	0	N.R.
(Blaszkowsky et al., 2014)	Phase I/II	32	LARC	3DCRT 50.4Gy/28	CT-RT (5-FU +BEV) + E	Overall 28% diarrhoea 18.8% rash 6.3%	0	21.8%
(Das et al., 2014)	Phase I	18	LARC	3DCRT 50.4Gy/28 fx	CT-RT (5-FU +BEV) + E	hypertension 5%	0	0
(Zhao et al., 2016)	Phase II	21	Inoperable ESCC	IMRT 60Gy/30 fx	CT-RT (weekly PAC) + E	esophagitis: 9% pneumonitis: 5%	0	N.R.

Ongoing trials

- Ongoing trial (soon open for accrual): **LAT FLOSI**
- UZ Leuven
- phase II prospective non-randomized observational trial
- Inclusion:
  - EGFR mutated advanced NSCLC
  - Osimertinib as a first-line treatment
  - LAT to ≤ 3 OP lesions (SABR or surgery)
  - stop TKI 3 days before, during and 3 days after SBRT/surgery to avoid interactions
- Primary endpoint: PFS

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Ongoing trials

- Other ongoing trials:

Trial	Study Design	n	Eligibility	Study Arms	Primary Endpoint	Expected results	Primary tumor
NRG LU 002 NCT03137771	Randomized phase II/III	300	NSCLC (≤3M+)	Maintenance therapy +/- SABR	Phase II: PFS Phase III: OS	2022	Primary tumor may be treated.
SARON NCT02417662	Randomized phase III	340	NSCLC (≤3M+)	Chemotherapy plus SABR vs chemotherapy alone	OS	2022	Primary tumor suitable for radical RT
SABR-COMET 10 NCT03721341	Randomized phase III	159	All (4-10 M+)	Standard of care +/- SABR	OS	2029	Controlled primary (3 months)
HALT NCT03256981	Randomized phase II/III	110	EGFR + NSCLC (Confirmed OPD ≤ 3 extracranial sites)	TKI +/- SABR	PFS	2021	Oligoprogressive disease

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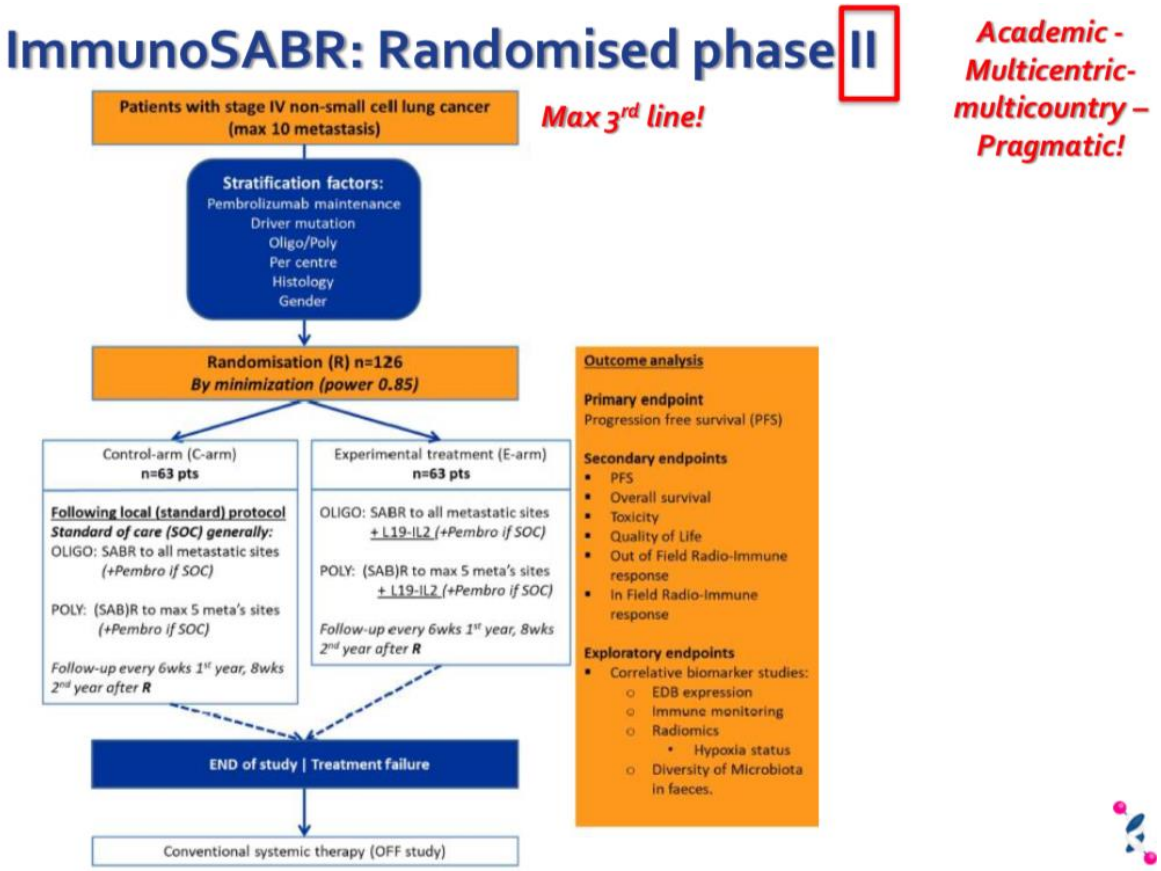
Ongoing trials

- ImmunoSABR = A Phase II study examining the activity of L19-IL2 immunotherapy and SABR in metastatic NSCLC



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RT in practice

- Preferable SABR

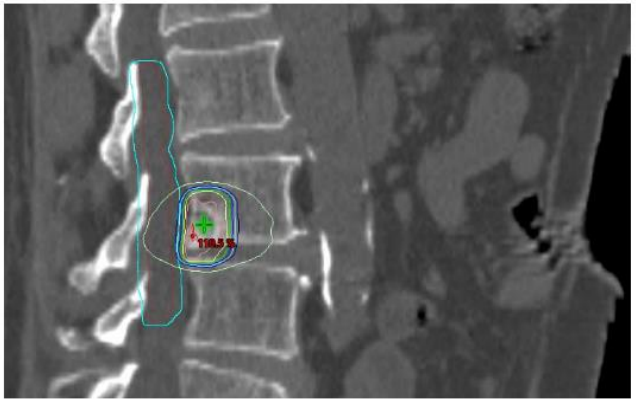
  = Three-dimensional high-precision technique to deliver a very high dose on a small volume, in one or a few irradiation fractions.

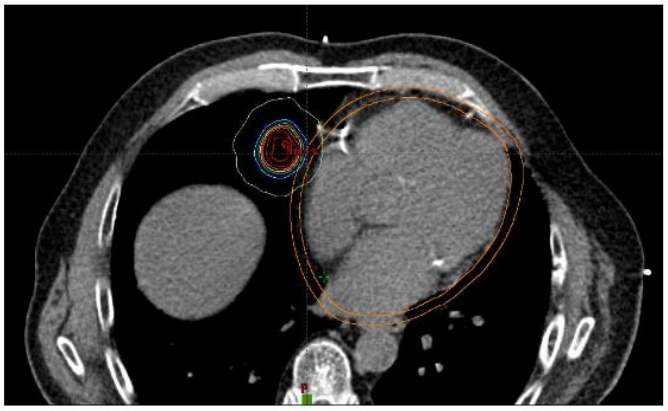
  Different fractionation schedules depending on nearby organs at risk

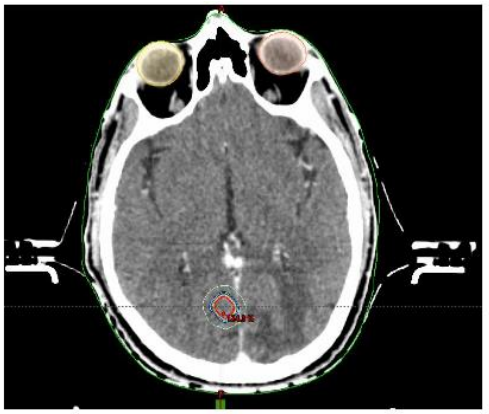
  1x 20 Gy

  3 x 10 Gy

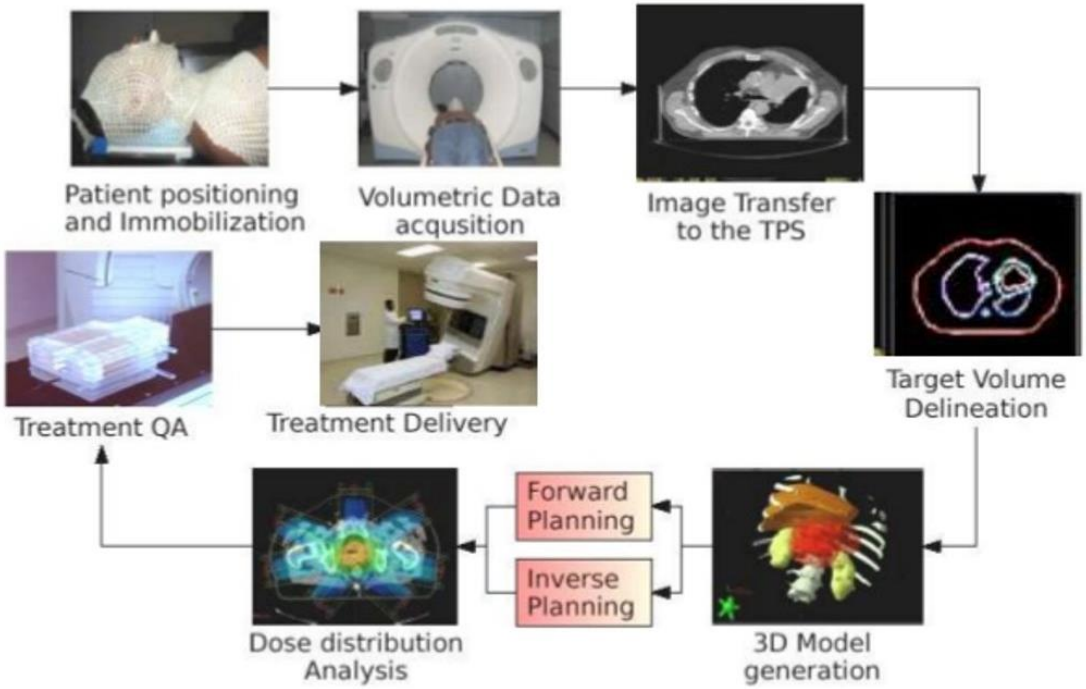
  5 X 7 Gy

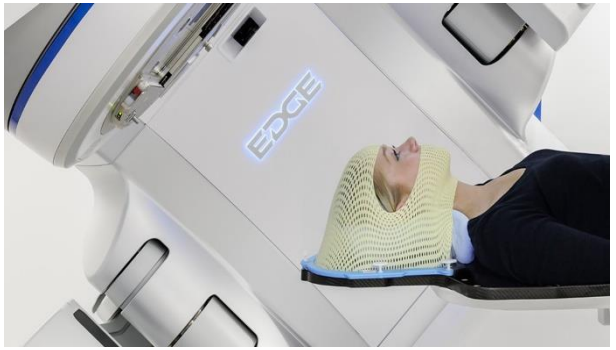


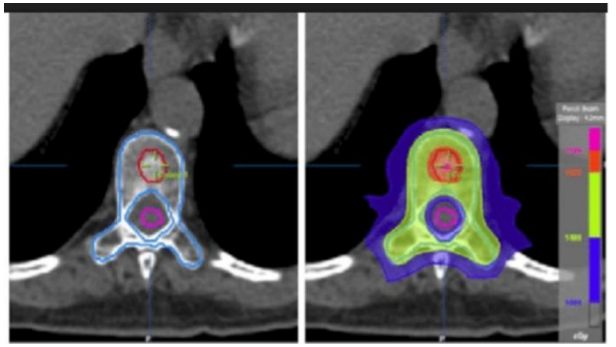


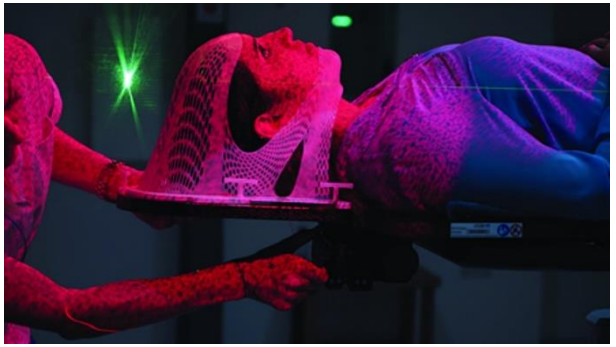


RT in practice









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Conclusions

- MTD likely benefits in different ‘oligo’ patients
- Promising results (however mainly phase II results)
- Many ongoing trials
- Future prospectives
  - Patient selection
  - Toxicity
  - Combination with systemic treatment (IO, targeted therapy)

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Thank you!

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