Memorial Sloan Kettering Cancer Center

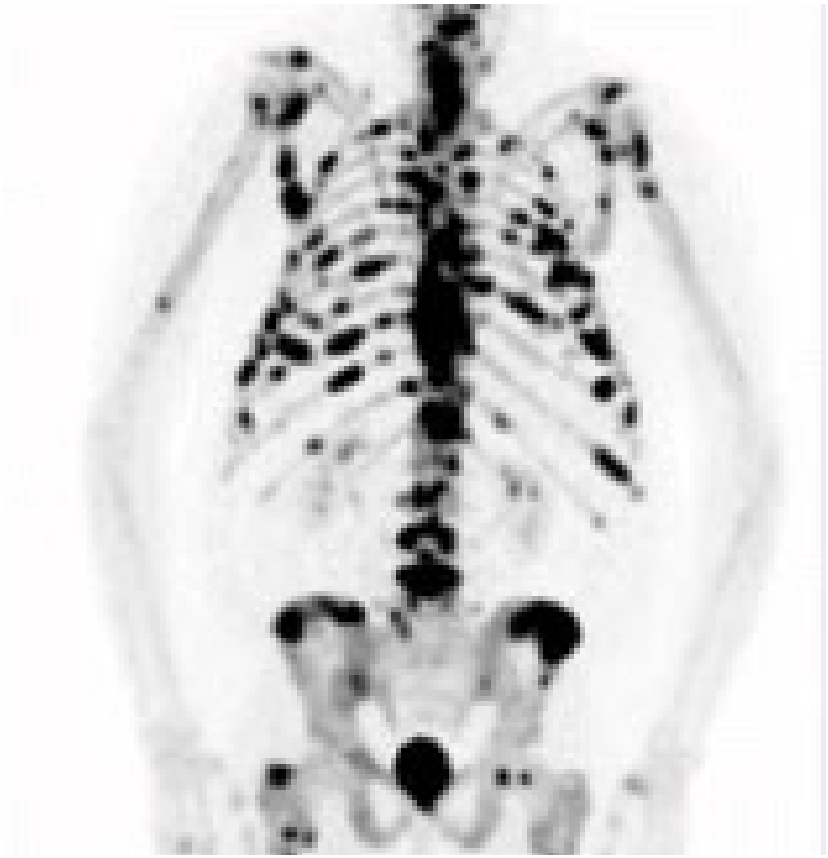
Ablative radiation in the treatment of oligometastatic cancers

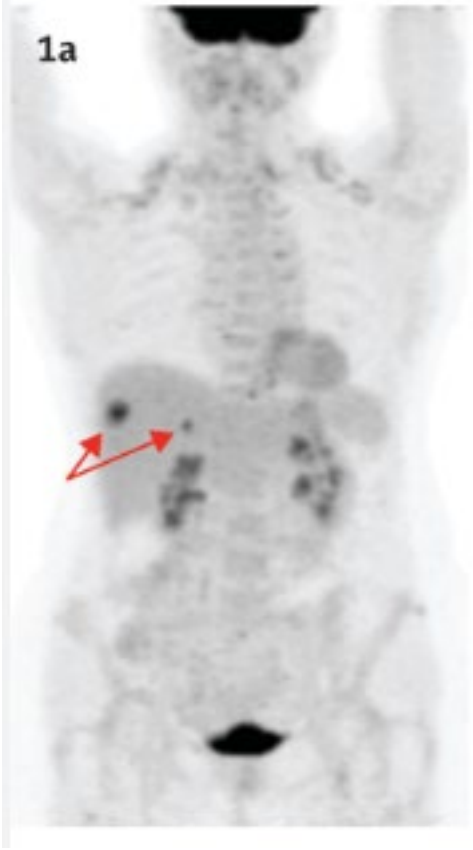
MSK Alliance APP Symposium
December 9th, 2022
David Guttmann, MD
Radiation Oncology, MSKCC

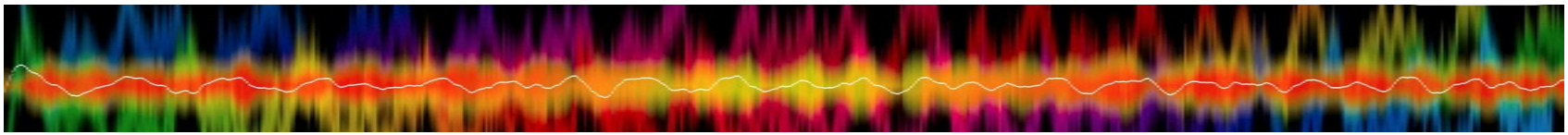
Summary

- Overview of the oligometastatic state
- Recent studies informing the use of radiation in oligometastatic disease
- Future considerations for focal therapy in metastatic cancers

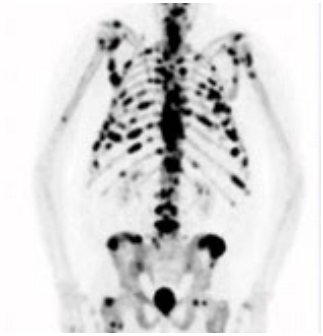
Metastatic disease is a continuum

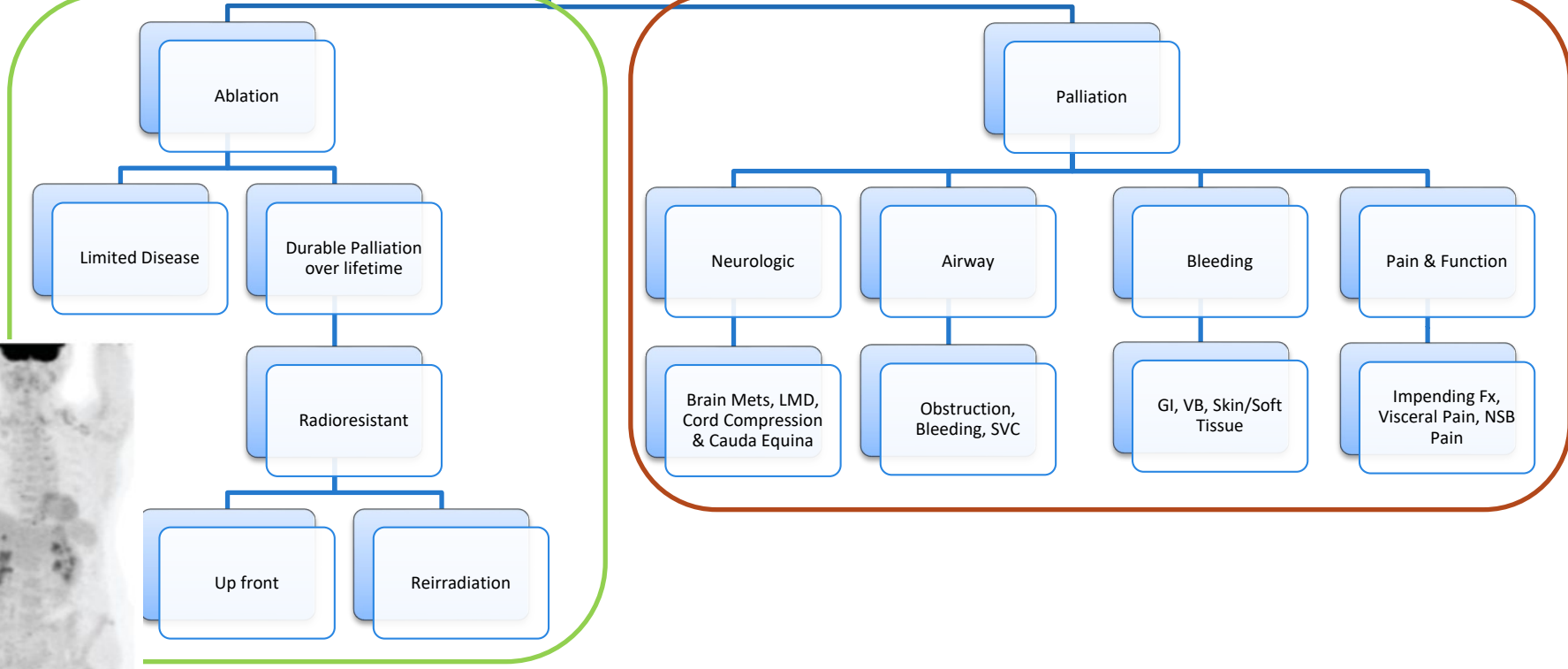






Paradigms of Metastatic Disease: Treatment Intent

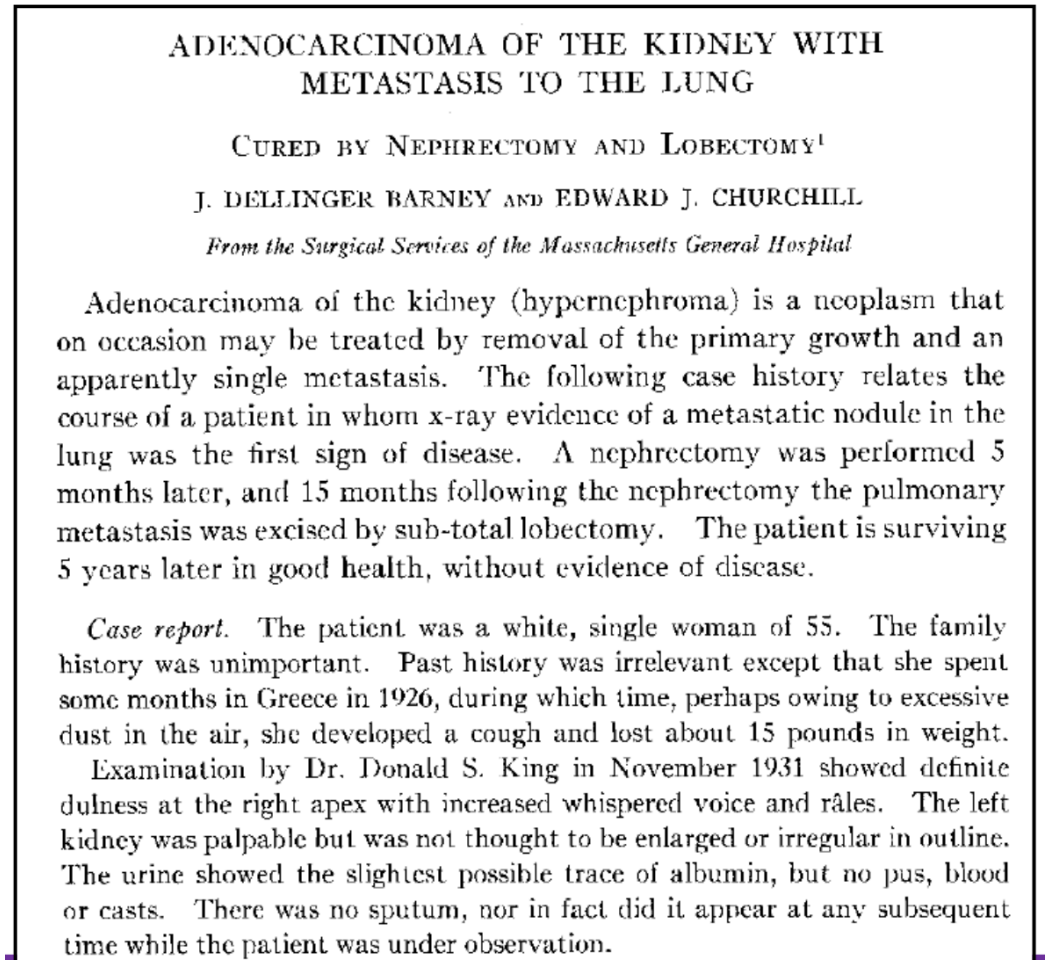




Courtesy of Divya Yerramilli, MD

Memorial Sloan Kettering Cancer Center

History – Oligometastatic disease in 1939



ADENOCARCINOMA OF THE KIDNEY WITH METASTASIS TO THE LUNG

CURED BY NEPHRECTOMY AND LOBECTOMY[1]

J. DELLINGER BARNEY AND EDWARD J. CHURCHILL

From the Surgical Services of the Massachusetts General Hospital

Adenocarcinoma of the kidney (hypernephroma) is a neoplasm that on occasion may be treated by removal of the primary growth and an apparently single metastasis. The following case history relates the course of a patient in whom x-ray evidence of a metastatic nodule in the lung was the first sign of disease. A nephrectomy was performed 5 months later, and 15 months following the nephrectomy the pulmonary metastasis was excised by sub-total lobectomy. The patient is surviving 5 years later in good health, without evidence of disease.

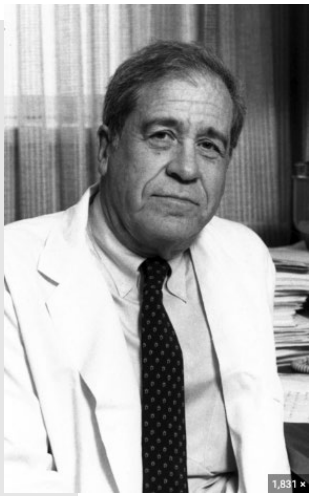
Case report. The patient was a white, single woman of 55. The family history was unimportant. Past history was irrelevant except that she spent some months in Greece in 1926, during which time, perhaps owing to excessive dust in the air, she developed a cough and lost about 15 pounds in weight.

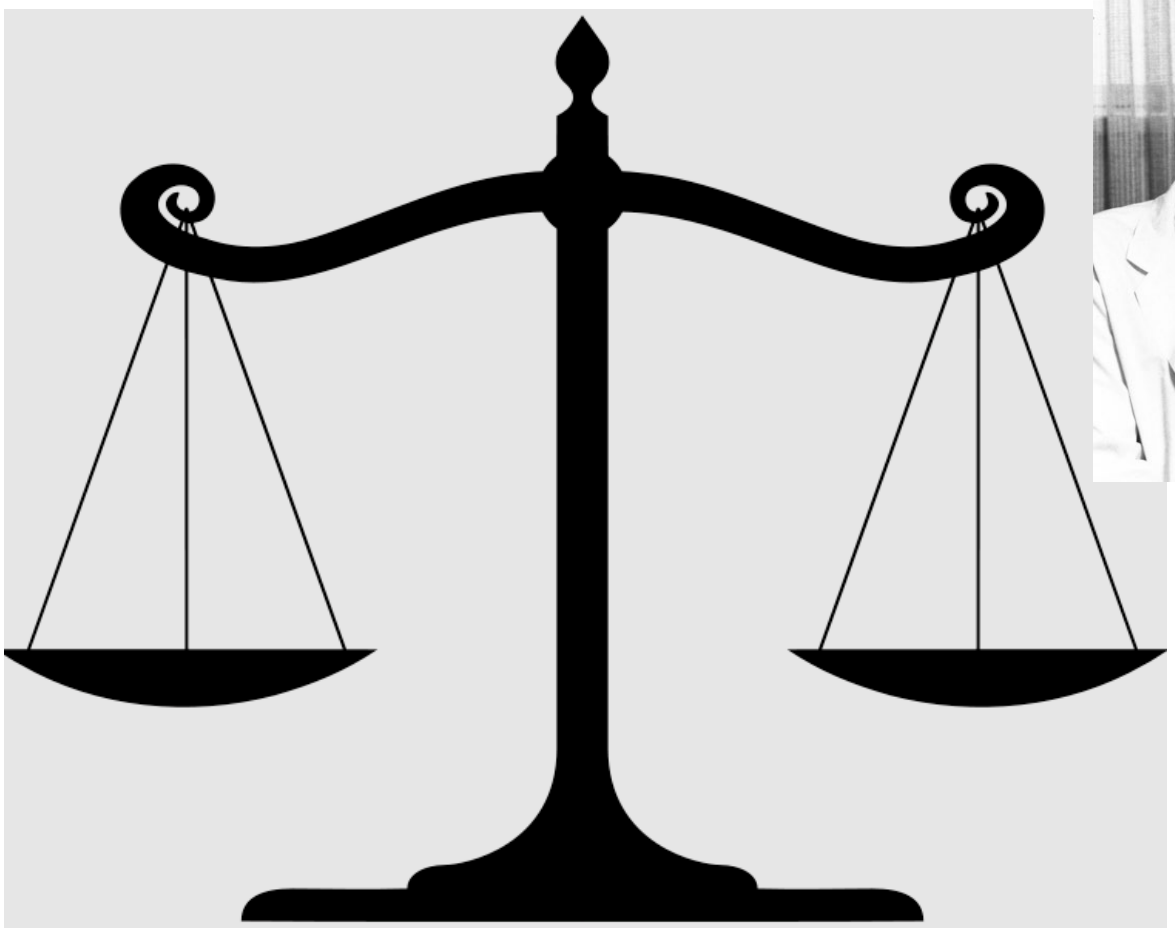
Examination by Dr. Donald S. King in November 1931 showed definite dulness at the right apex with increased whispered voice and râles. The left kidney was palpable but was not thought to be enlarged or irregular in outline. The urine showed the slightest possible trace of albumin, but no pus, blood or casts. There was no sputum, nor in fact did it appear at any subsequent time while the patient was under observation.

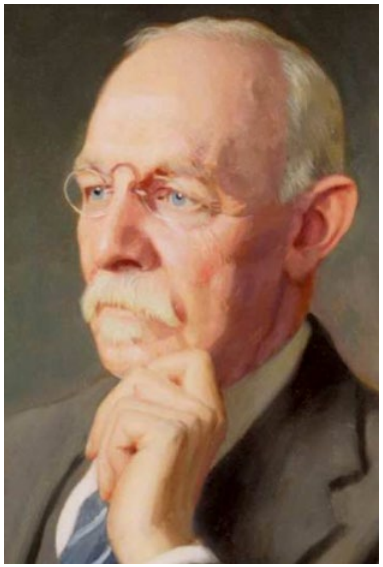
"if a metastasis is apparently solitary and accessible to surgical removal, it is definitely worthwhile to undertake removal of the metastasis as well as the primary growth."

Cancer as a local vs. systemic disease

Bernard Fischer, MD





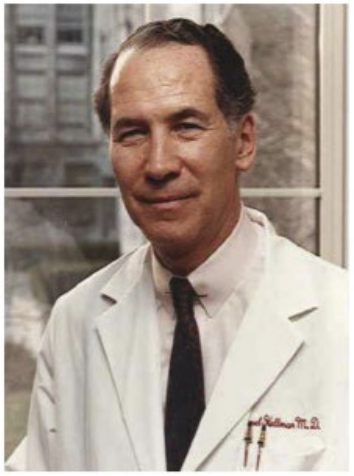


William Halstead, MD

"breast cancer is a systemic disease . . . and that variations in effective local regional treatment are unlikely to affect survival substantially."

Oligometastatic Disease Defined

- Weichselbaum & Hellman proposed an intermediate disease state between locoregional spread and widely metastatic disease:
  - Limited by site/number
  - Potentially “curative”



Dr. S. Hellman

Dr. R. Weichselbaum

EDITORIAL

Oligometastases

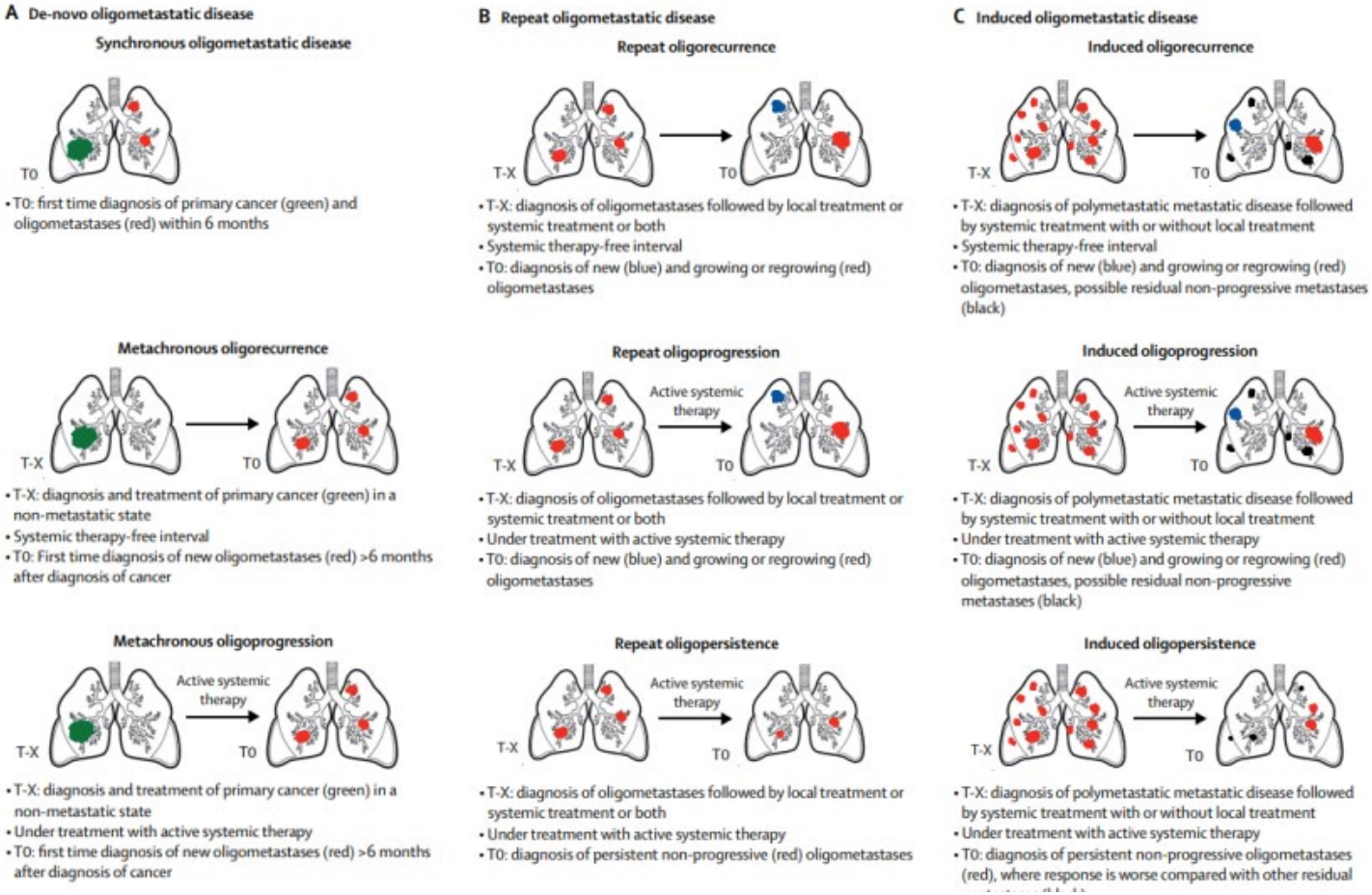
CANCER TREATMENT is based on an often unstated paradigm of disease pathogenesis. Since 1894, when W.S. Halsted[1,2] clearly elucidated a mechanism of breast cancer spread and used it to design and support the radical mastectomy, surgical and radiotherapeutic approaches to most cancers have been based on this theory. The Halsted theory proposed that cancer spread is orderly, extending in a contiguous fashion from the primary tumor through the lymphatics to the lymph nodes and then to distant sites. Radical en bloc surgery, such as radical neck dissection in continuity with removal of the primary tumor, radical hysterectomy, and primary and regional irradiation for a variety of tumor sites are all based on this notion of cancer spread. More recently, another hypothesis has gained prominence, also first suggested more about the multistep nature of the development of malignancy.[11-13] Once tumors become invasive, they may gradually acquire the properties necessary for efficient and widespread metastatic spread.[14] Therefore the likelihood, number, and even sites of metastases may reflect the state of tumor development. This suggests that there are tumor states intermediate between purely localized lesions and those widely metastatic. Such clinical circumstances are not accounted for by either the contiguous or the systemic hypotheses. The systemic hypothesis is binary: metastases either do or do not exist. If present, even if microscopic, they are extensive and widespread. The contiguous hypothesis considers systemic metastases to occur only after nodal disease; but when they occur, they are also blood borne, extensive, and widespread.

Hellman, S. & Weichselbaum, R. R. Oligometastases. J. Clin. Oncol. 13, 8–10 (1995).

Memorial Sloan Kettering Cancer Center

Adapted from Divya Yerramilli, MD

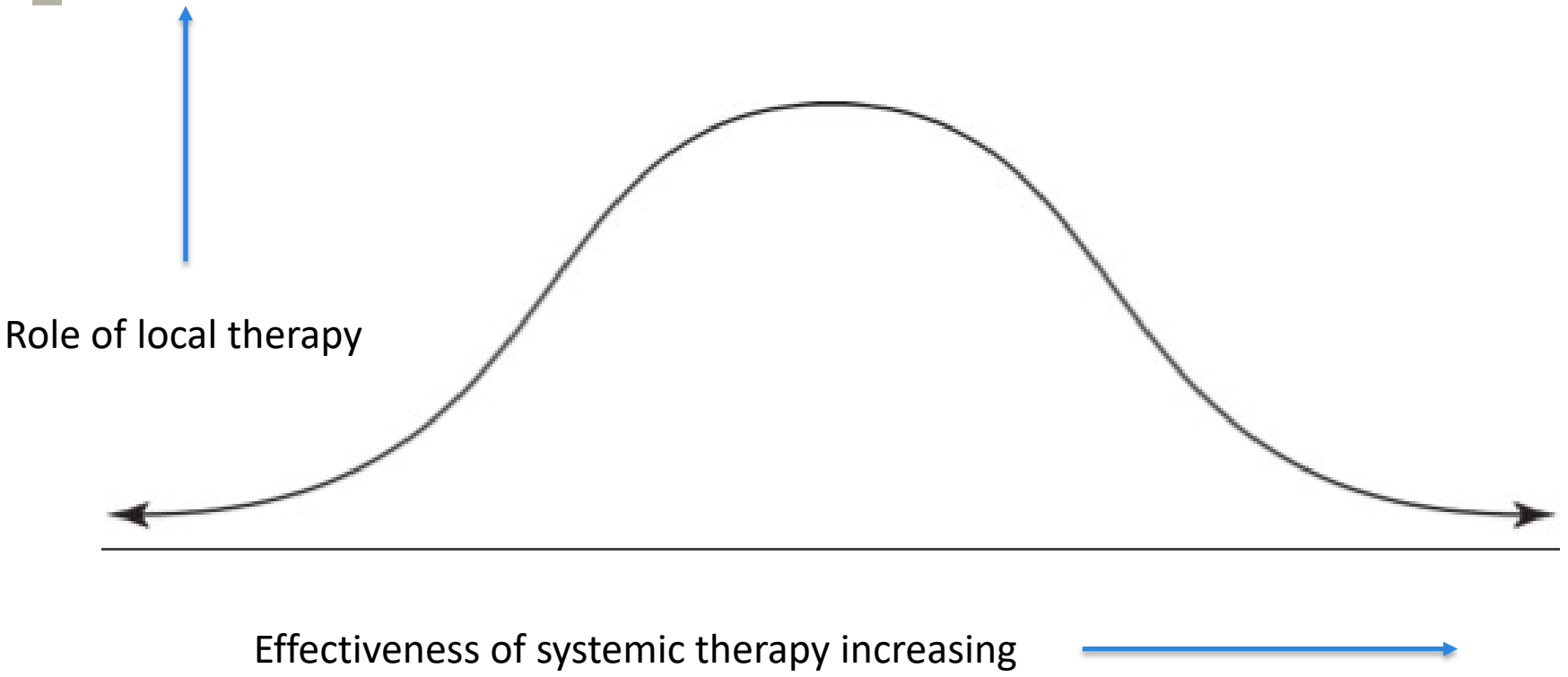
Distinguishing Different Oligometastatic States – ESTRO/EORTC



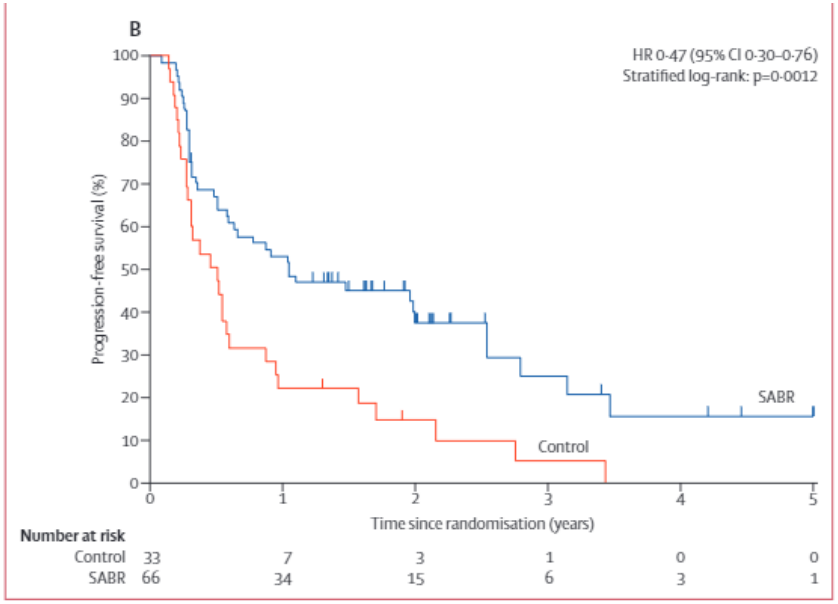
Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation

Memorial Sloan Kettering Cancer Center

Why is there increasing interest in oligometastatic disease?



SABR-COMET: Systemic therapy +/- local treatment to oligomets in all histologies



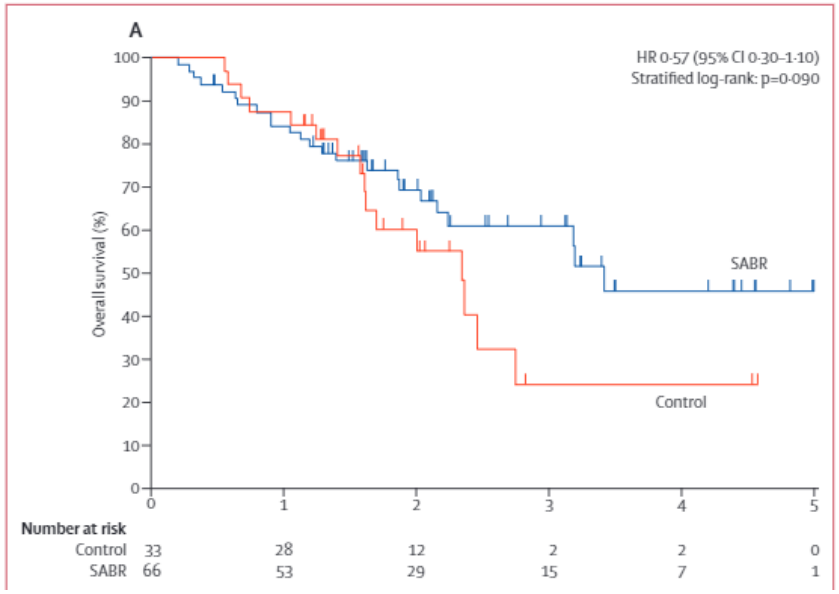


Figure 2: **Overall survival (A) and progression-free survival (B)**
SABR=stereotactic ablative radiotherapy. HR=hazard ratio.

Palma DA, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. The Lancet. 2019 May 18;393(10185):2051-8.

Memorial Sloan Kettering Cancer Center

Oligomez: NSCLC, induction systemic therapy+/- local consolidation

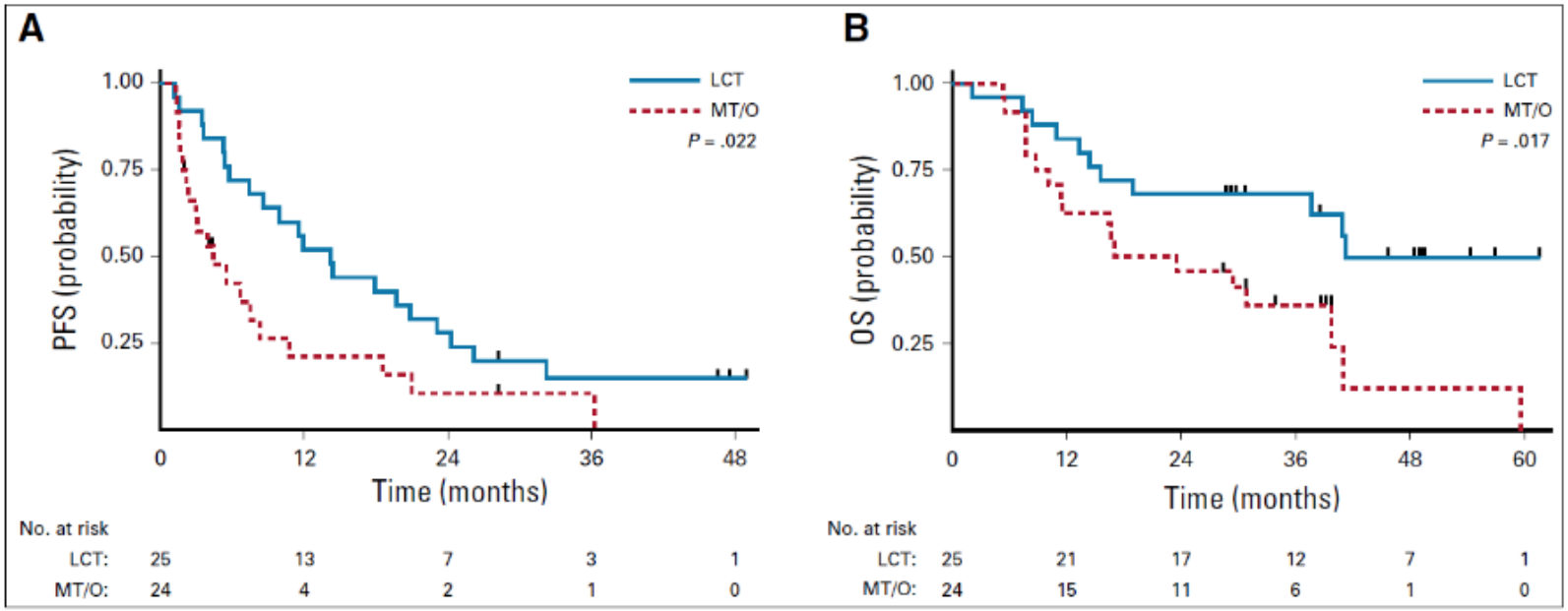


FIG 1. (A) Progression-free survival (PFS) and (B) overall survival (OS) in patients given local consolidative therapy (LCT) or maintenance therapy or observation (MT/O) for oligometastatic non–small-cell lung cancer.

Gomez et al., Lancet Oncol. 2016 Dec;17(12):1672-1682.

Memorial Sloan Kettering Cancer Center

SINDAS: EGFR-mutated NSCLC

Randomized Trial of First-Line Tyrosine Kinase Inhibitor With or Without Radiotherapy for Synchronous Oligometastatic *EGFR*-Mutated NSCLC

Figure 2

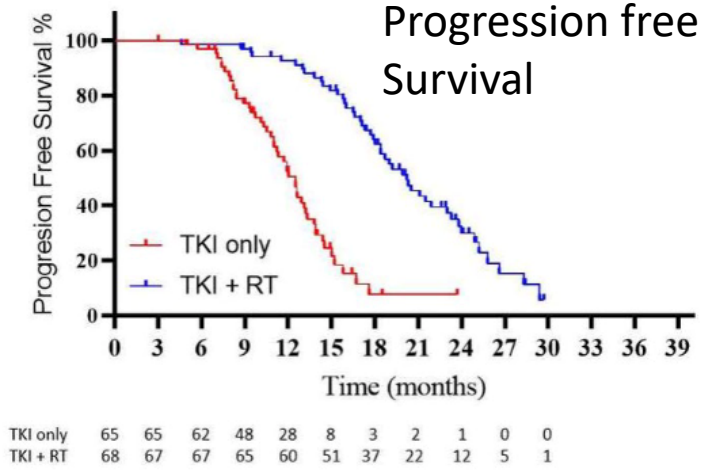
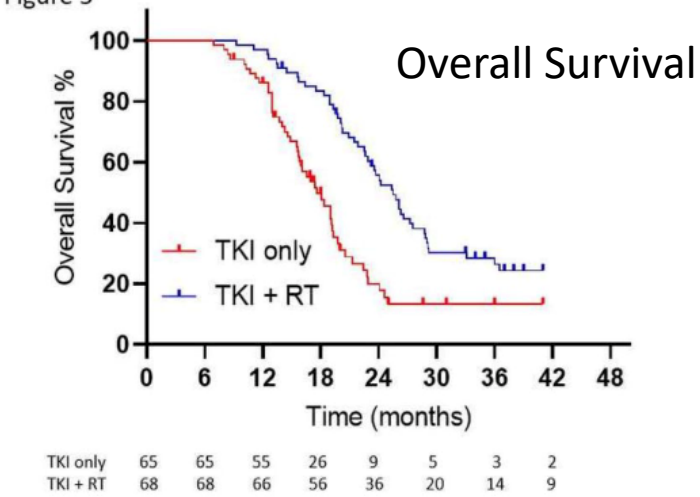
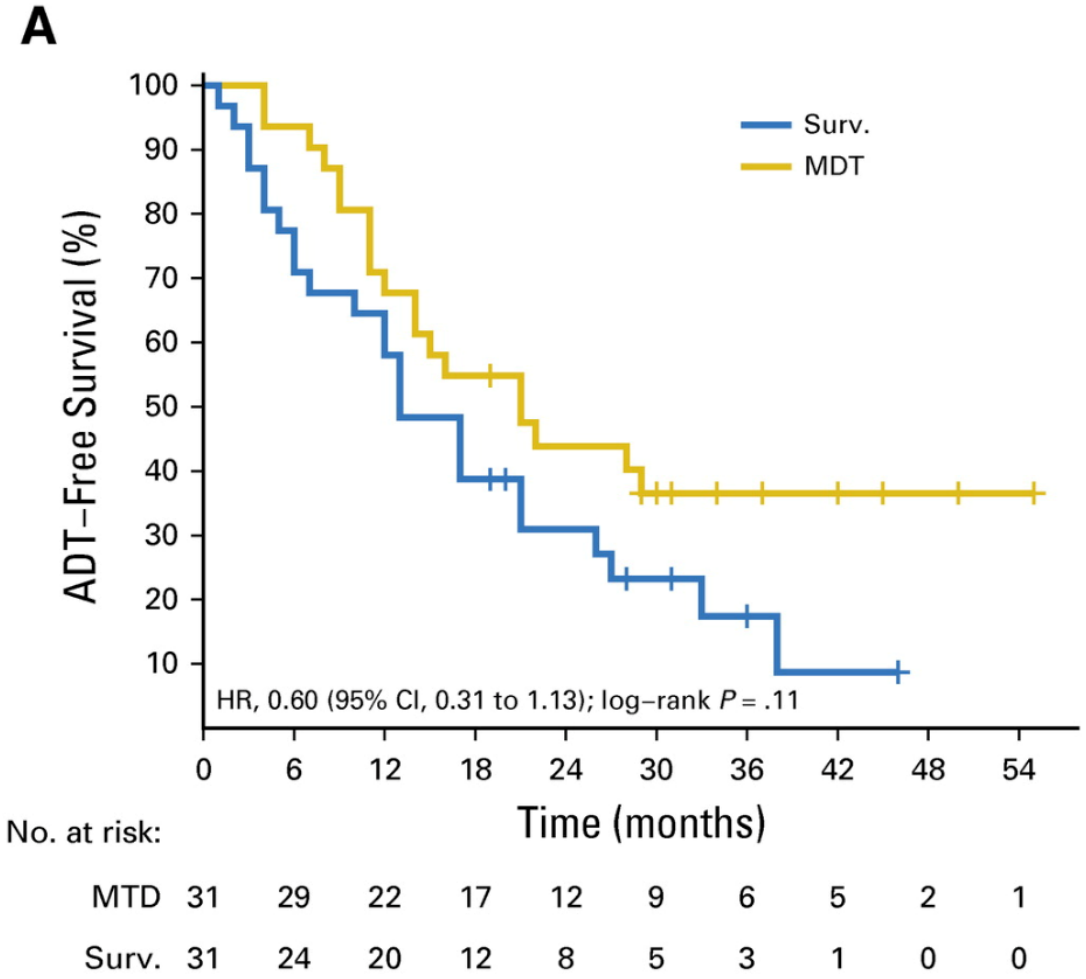


Figure 3



Wang et al, JNCI 2022

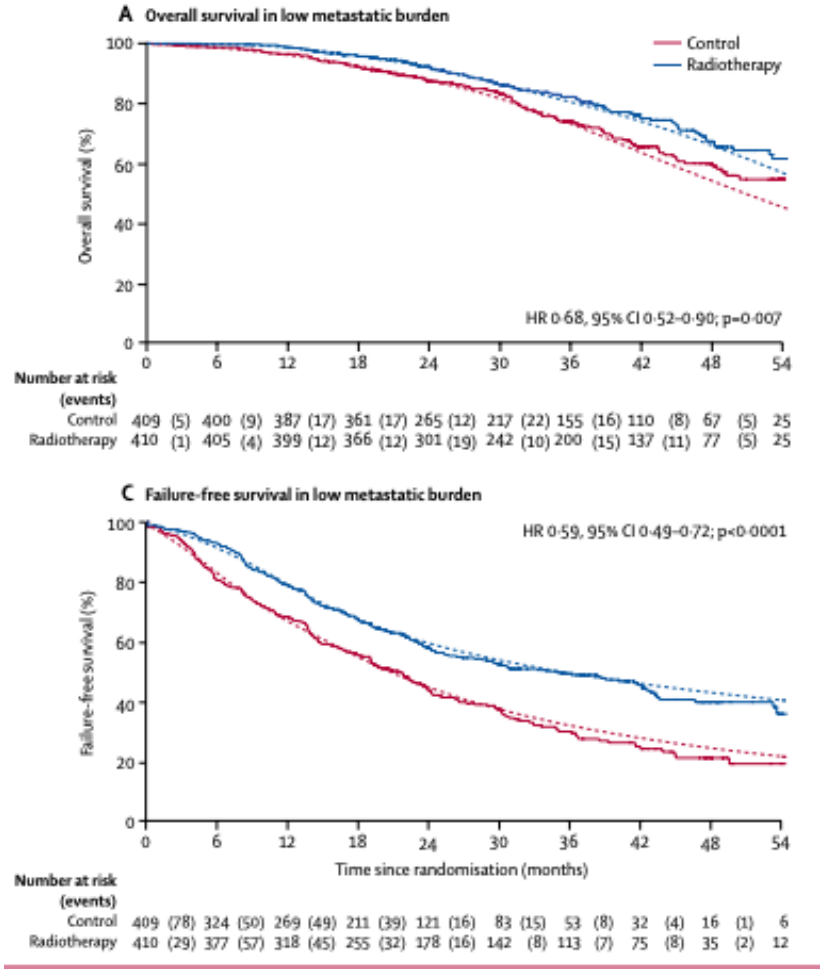
STOMP: SBRT can delay initiation of ADT in metastatic prostate cancer



Ost et al., J Clin Oncol. 2018 Feb 10;36(5):446-453.

Memorial Sloan Kettering Cancer Center

Treatment of the primary site in oligometastatic disease: Prostate Cancer



Parker et al., Lancet. 2018 Dec 1;392(10162):2353-2366.

Memorial Sloan Kettering Cancer Center

SBRT for oligometastatic disease in the UK System

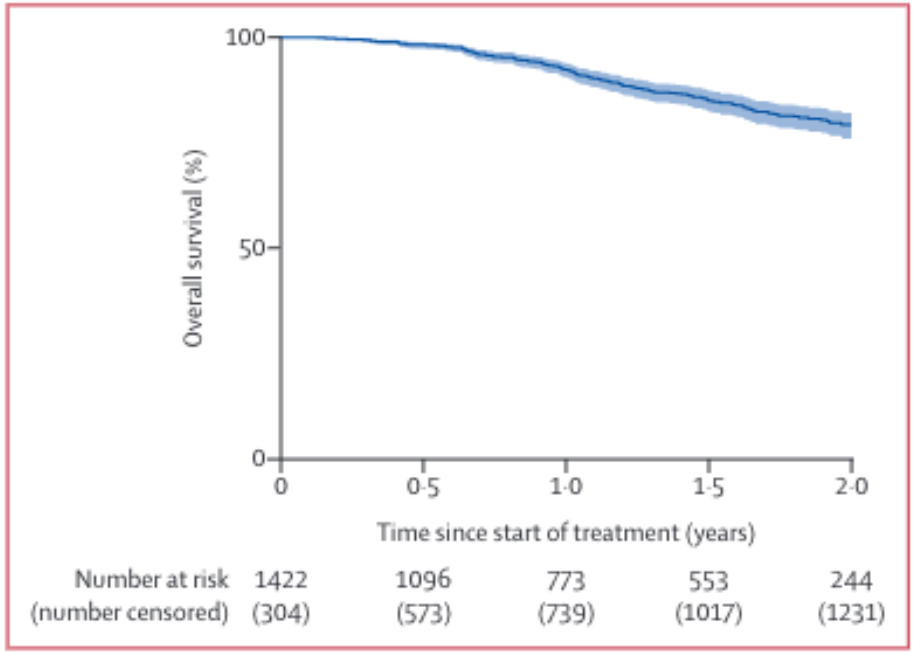


Figure 1: **Kaplan-Meier analysis of overall survival in the total cohort**
Shaded areas represent 95% CIs.

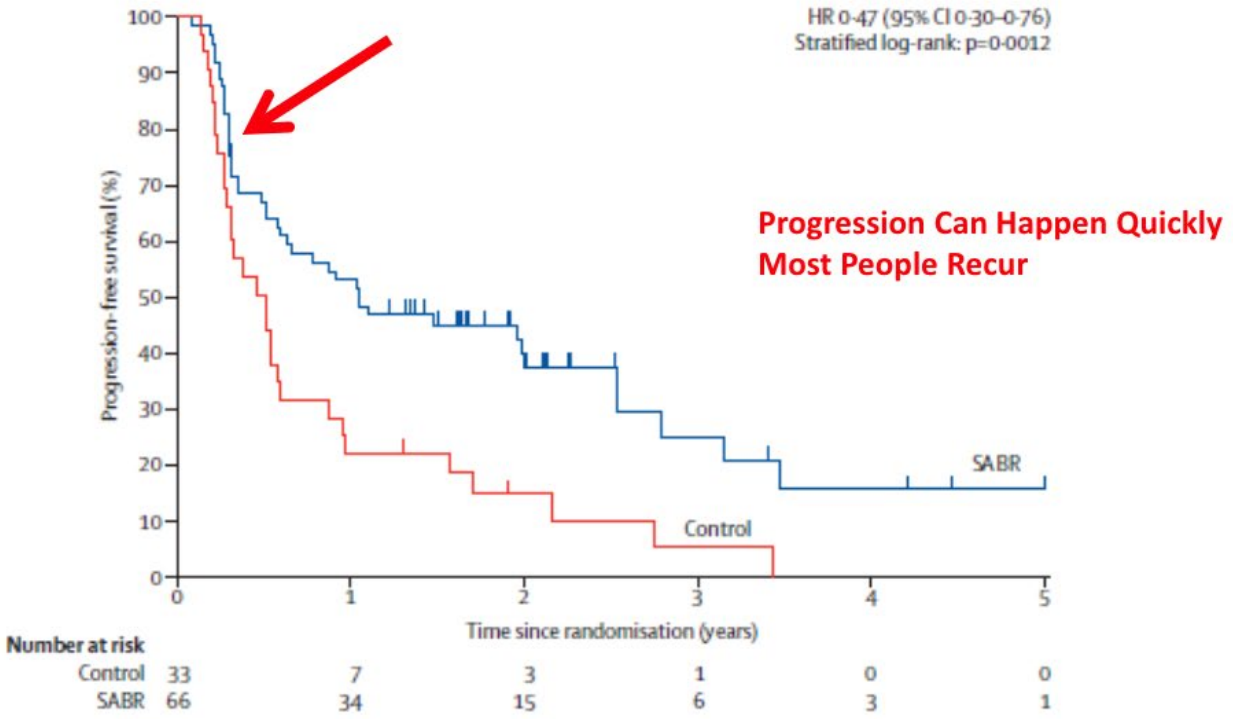
	Grade 1–2	Grade 3	Grade 4
Fatigue	775 (55%)	28 (2%)	0
Cough	221 (16%)	7 (<1%)	0
Urinary frequency	167 (12%)	0	0
Nausea	147 (10%)	3 (<1%)	0
Spinal fracture	144 (10%)	2 (<1%)	0
Urinary urgency	126 (9%)	0	0
Urinary incontinence	100 (7%)	1 (<1%)	0
Diarrhoea	95 (7%)	2 (<1%)	0
Pneumonitis	93 (7%)	2 (<1%)	0
Dysphagia	87 (6%)	2 (<1%)	0
Gastritis	61 (4%)	0	0
Rectal haemorrhage	43 (3%)	0	0
Proctitis	39 (3%)	0	0
Bone pain	35 (2%)	6 (<1%)	0
Myelitis	33 (2%)	0	0
Haematuria	27 (2%)	1 (<1%)	0
Pericarditis	23 (2%)	2 (<1%)	1 (<1%)
Urinary retention	23 (2%)	0	1 (<1%)
Vomiting	17 (1%)	2 (<1%)	0
Gastrointestinal haemorrhage	12 (1%)	3 (<1%)	0
Fever	11 (1%)	1 (<1%)	0
Alanine aminotransferase increase	11 (1%)	3 (<1%)	2 (<1%)
Bilirubin increase	10 (1%)	8 (1%)	7 (<1%)
Upper gastrointestinal ulcer	9 (1%)	0	0
Duodenal or gastric ulcer	7 (<1%)	1 (<1%)	0
Fracture	5 (<1%)	0	0
Fistula	3 (<1%)	0	0
Perforation	1 (<1%)	0	0

Adverse events occurring in at least 10% of patients and all grade 3 and 4 events are reported. Data are aggregated at the patient level as n (%; n=1422), with events reported at consecutive follow-up visits counted once and maximum grade reported per event per patient. Patients with more than one event are listed for each event. There were no deaths due to adverse events.

Table 3: **Treatment-related adverse events**

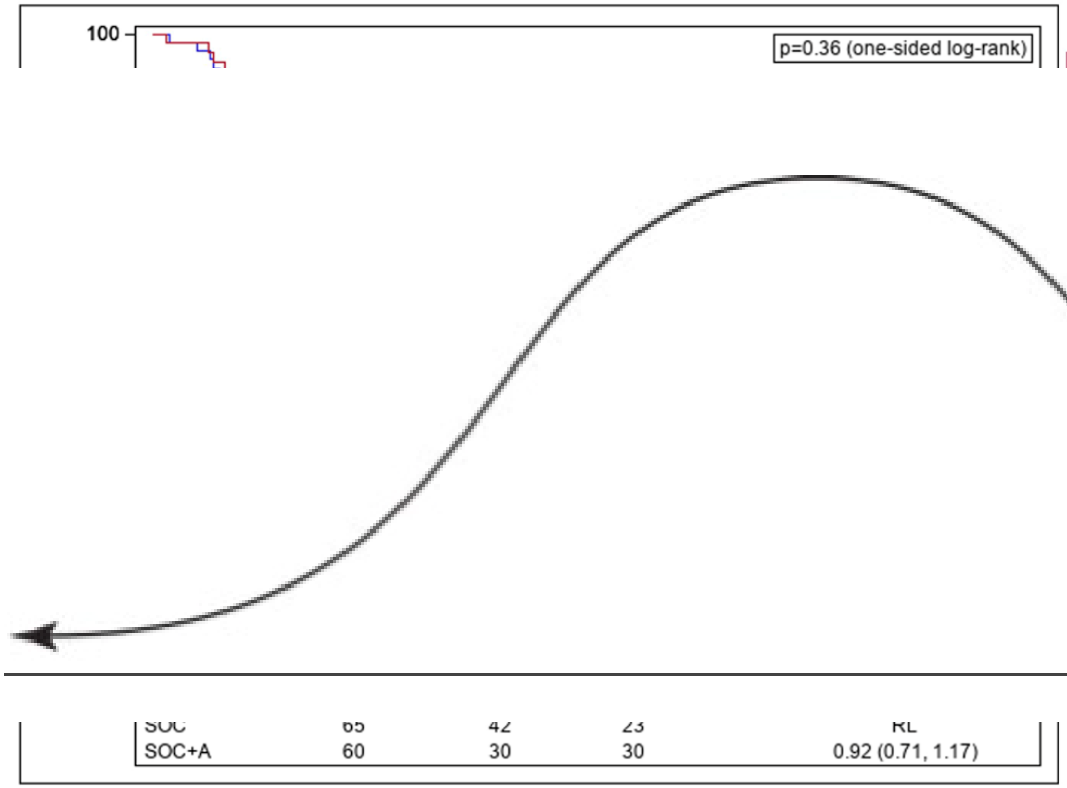
Chalkidou A, Macmillan T, Grzeda MT, et al. Stereotactic ablative body radiotherapy in patients with oligometastatic cancers: A prospective, registry-based, single-arm, observational, evaluation study. *Lancet Oncol.* 2021;22:98-106

SABR is Usually Not Curative



Progression Can Happen Quickly
Most People Recur

A Cautionary Tale – NRG BR 002



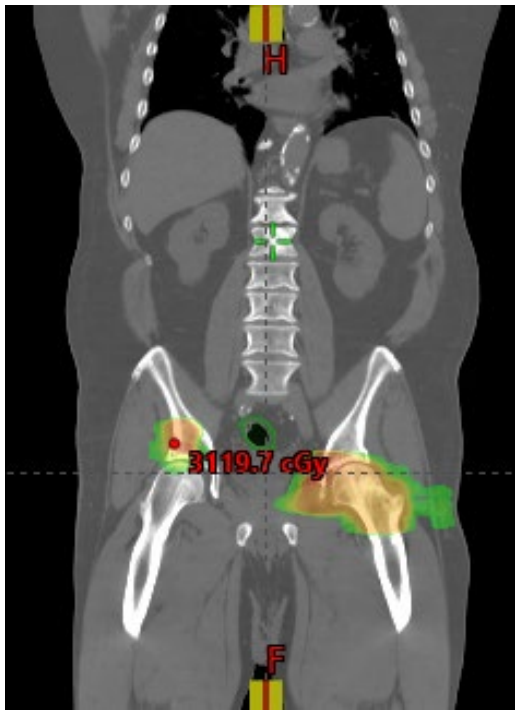
Median Follow-up = 35 months
(min-max: 0.03-62.74)

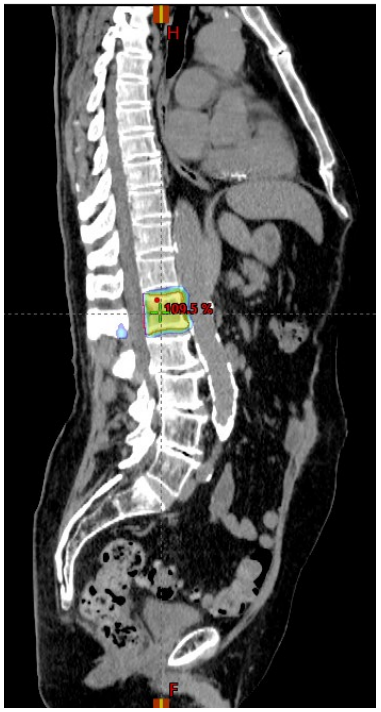
Chmura et al., ASCO 2022

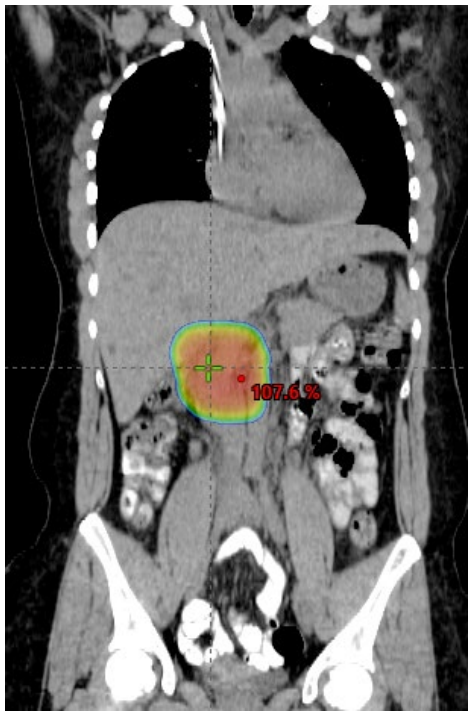
Is this approach cost effective?

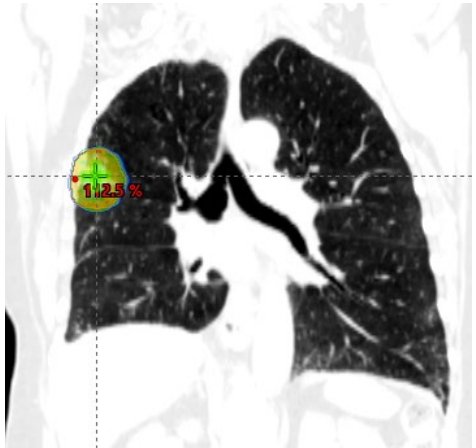
- Yes!
  - ICER for SBRT ~$40k vs. ~$200k for certain systemic therapies per QALY
- Per year, medicare pays more for pemrolizumab and nivolumab than for all radiation therapy services combined

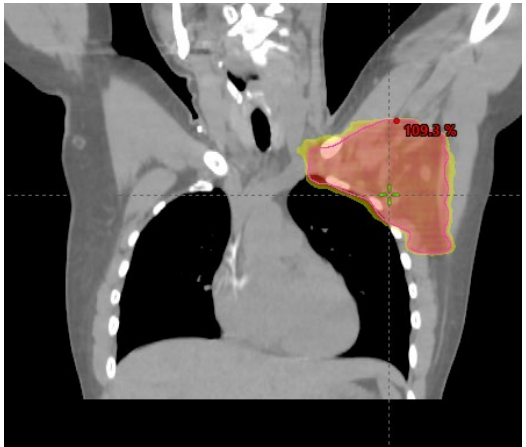
Ablative Radiation Techniques









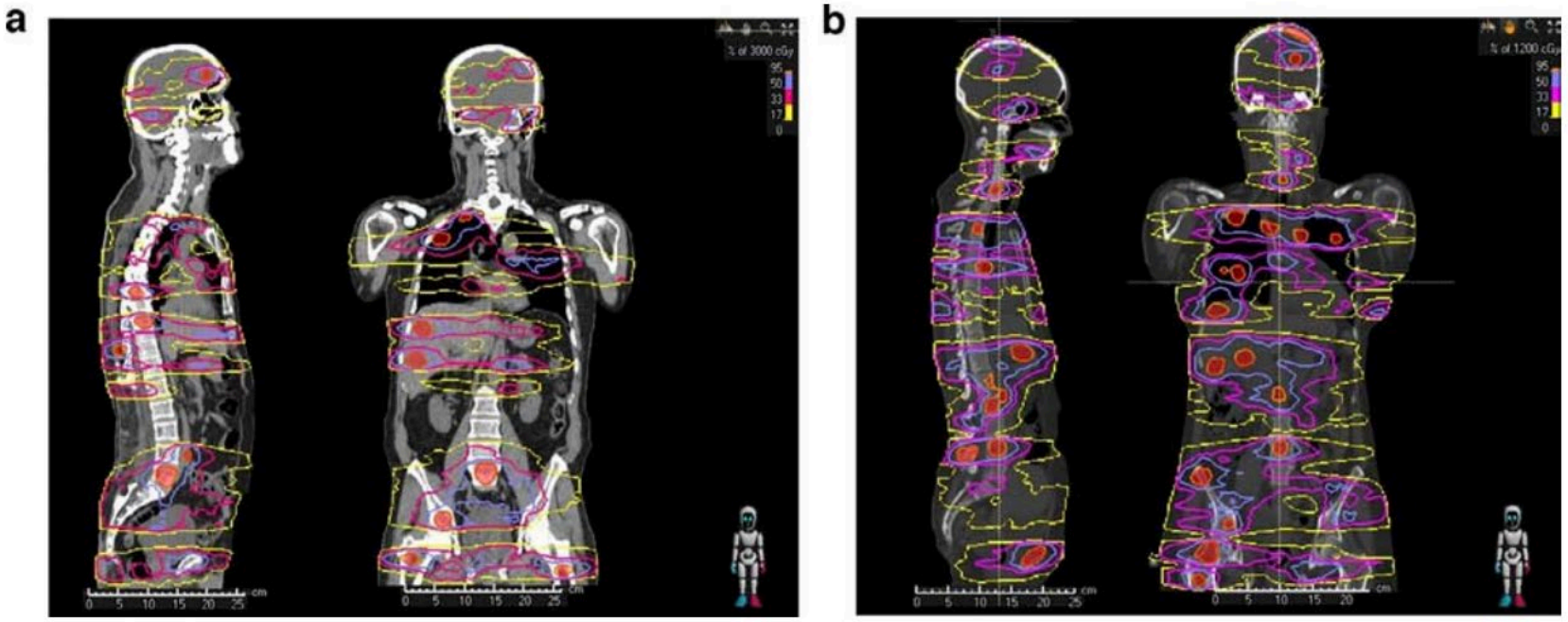


Memorial Sloan Kettering Cancer Center

Future directions

- Better defining oligometastatic disease
  - Number of mets?
  - Total metastatic volume?
  - Circulating tumor DNA?
  - Histology-specific considerations?
- Expanding role of local therapy to the polymetastatic state

Local therapy for polymetastatic disease? – Phase I study in progress



Corcum et al, ARO 2021

Questions?

Patient selection is key

	Patient selection	Toxicity risk	Timing
Best candidates	Good performance status Low burden of disease (one oligometastasis) Multiple systemic therapy options	Small lesions Treatment unlikely to cause toxicity (eg, small resection or tumor far from critical structures)	Metachronous oligometastases Responding to systemic therapy
Less favorable	Borderline performance status (eg, ECOG 2) Moderate burden of disease (two to five oligometastases)	Larger lesions Moderate risk of toxicity or impact on organ function	Synchronous oligometastases Overlapping toxicities (eg, immunotherapy and thoracic radiotherapy)
Unfavorable	Poor performance status High burden of disease (> 5 metastases)	Very large lesions High risk of toxicity Comorbidities precluding radiotherapy or surgery	No response to systemic therapy Rapid disease progression

Jasper et al, JCO 2022