STEREOTATIC BODY RADIATION THERAPY (SBRT) FOR OLIGOMETASTATIC BREAST CANCER - PRO

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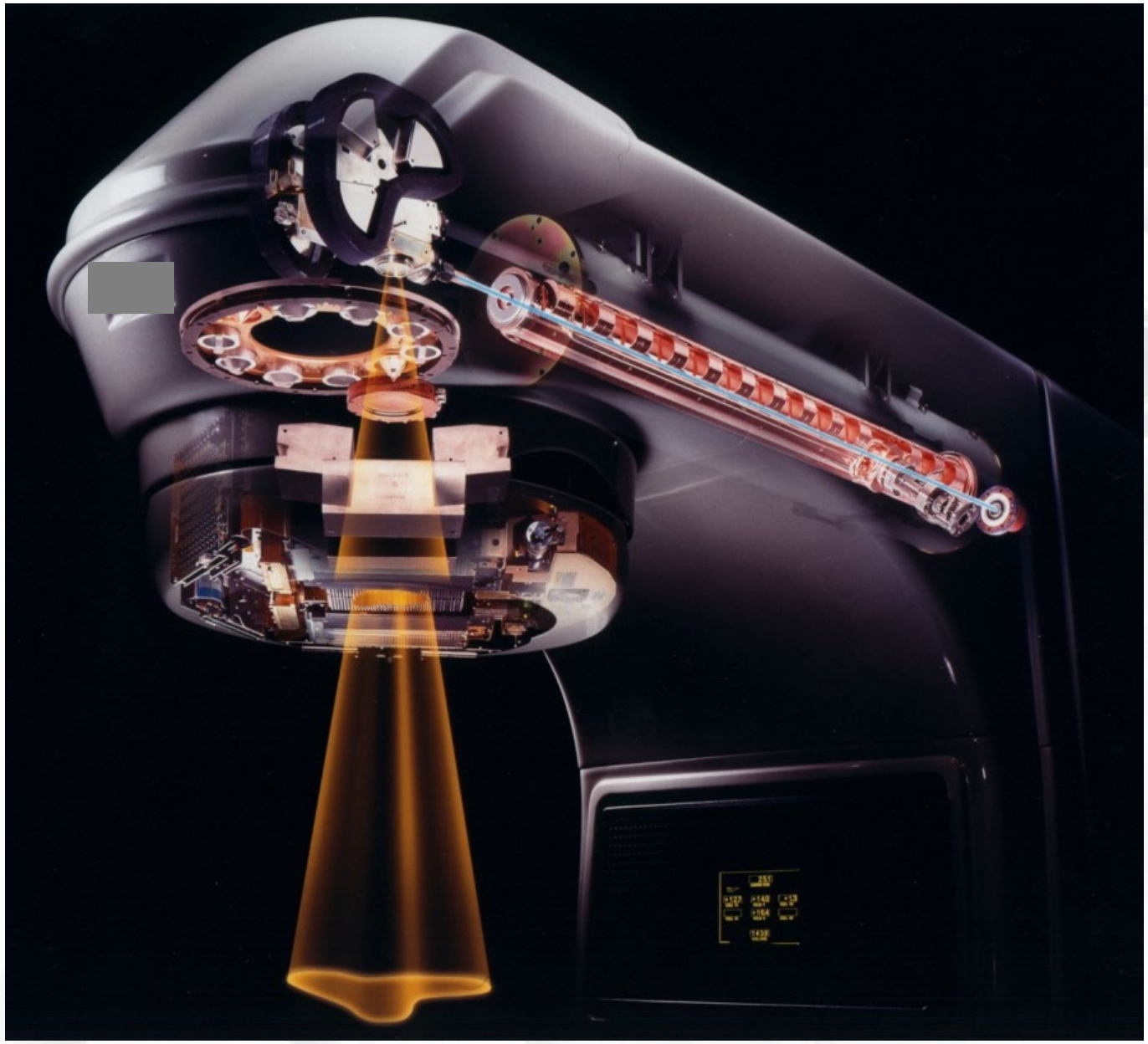

AGENDA

1. Background
2. Stereotactic body radiation therapy (SBRT) for oligometastatic disease
3. SBRT for oligometastatic breast cancer
4. Ongoing randomized clinical trials
5. Logistics of SBRT

OLIGOMETASTATIC DISEASE

- In 1995, Hellman and Weichselbaum proposed the idea of an oligometastastic state in patients with limited metastases
  - "For certain tumors, the anatomy and physiology may limit or concentrate these metastases to a single or a limited number of organs"
    - Some patients may be "amenable to a curative therapeutic strategy"
      - Surgical excision
      - Ablation with radiation therapy (RT)
- No uniform definition of what is oligometastatic (OM) disease
  - Often defined as up to 3 sites and 5 lesions
  - ESTRO-ASTRO convened a committee to establish a consensus document
    - Maximal number of lesions must be limited by the ability to deliver safe, curative intent metastasis-directed RT – varies on a case-by-case basis

Hellman S and Weichselbaum RR. J Clin Onc 13:8-10, 1995
Lievens Y et al. Radiotherapy and Oncology 148:157-166, 2020

IMPORTANT ENDPOINTS TO CONSIDER:

- Overall survival (OS)
- Disease-free survival (DFS) or progression-free survival (PFS)
- Local control (LC)
- Toxicity
- Quality of life (QoL)
- Patient-reported outcome measures
- Cost
- Delay or deferral of systemic therapy
- Ability to stay on the same line of systemic therapy

Lievens Y et al. Radiotherapy and Oncology 148:157-166, 2020

SBRT FOR OLIGOMETASTATIC DISEASE

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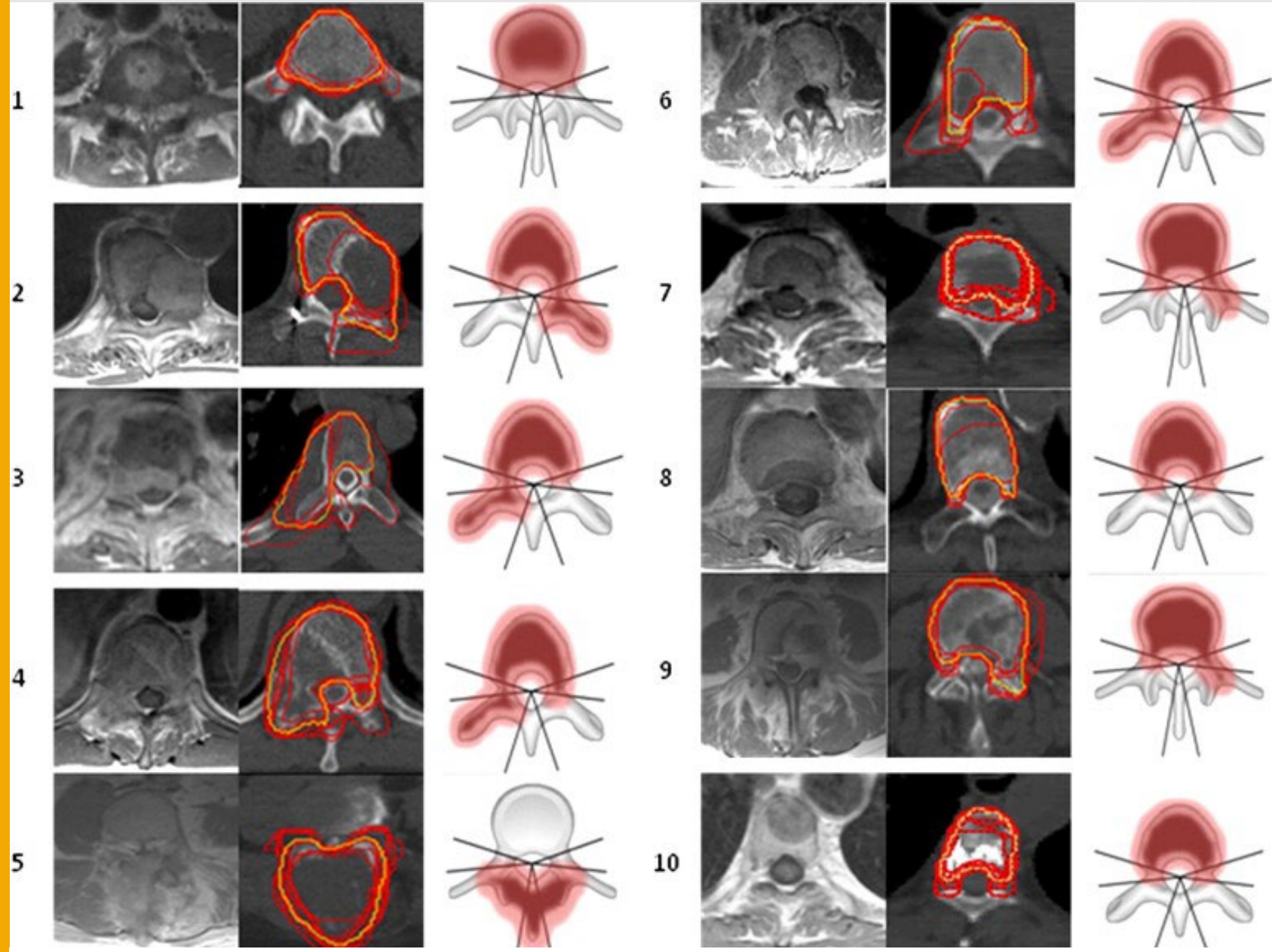


Consensus clinical target volume contours for spinal stereotactic radiosurgery. Red indicates individual contours and orange indicates consensus contours.

Cox BW, et al. IJROBP (2012) 83:e597-605

SBRT/SABR

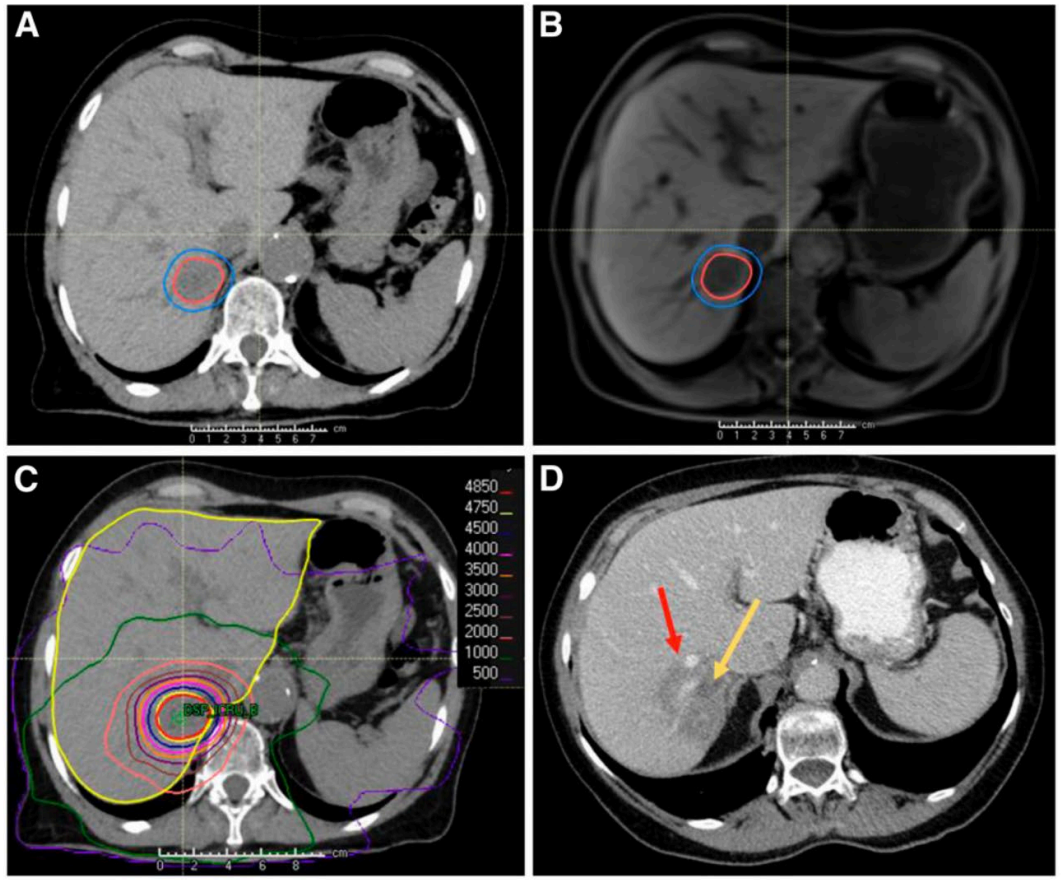


FIGURE 1. Stereotactic Body Radiation Therapy Case Study

(A) CT simulation demonstrating the gross tumor volume (GTV; red) and planning target volume (PTV; blue). (B) MRI simulation (T1-weighted MRI) demonstrating the GTV (red) and PTV (blue). MRI was obtained to aid in target volume definition in this case. (C) Axial CT slice demonstrating the isodose distribution for an SBRT plan delivering 45 Gy in five fractions (BED_{10}, 85.5 Gy). (D) Diagnostic CT obtained at 3 months after treatment. Response is seen within the treated lesion (yellow arrow) and radiation-related change is seen in the surrounding tissue (red arrow) corresponding to the low isodose lines.

Uhlig J, et al. ASCO Education Book 2021;41:133-146.

Non-invasive approach using precise, high dose RT to target & ablate tumor

- May be an alternative for patients with:
  - Co-morbidities precluding resection
  - Technically inoperable lesion(s)
  - Lesions not amenable to other local therapy such as ablation

- SBRT has steep dose gradients that can be centered near tumor edge
  - Limits dose delivered to surrounding normal tissue and nearby organs
  - High rates of local control
  - Usually given in few fractions (ie 1-5 fractions, depending on location, tumor size, nearby organs, etc)

SABR-COMET TRIAL

- An international Phase 2 randomized trial comparing palliative standard-of-care (SOC) treatment to SOC + SBRT in patients with oligometastatic disease
  - Patients must have controlled primary malignancy and 1-5 metastatic lesions, with all metastatic lesions amenable to SBRT
    - Randomized in 1:2 ratio between SOC vs SOC+SBRT
      - Stratified by number of mets (1-3 vs 4-5)
  - Primary endpoint: overall survival
  - Accrued and randomly assigned 99 patients
    - Treated between 2012 – 2016
    - Most common primary tumor types were breast (n=18), lung (n=18), colorectal (n=18), and prostate (n=16)
    - Median follow-up 51 months

Palma DA, et al. J Clin Oncol (2020) 38:2830-2838

SABR-COMET TRIAL RESULTS

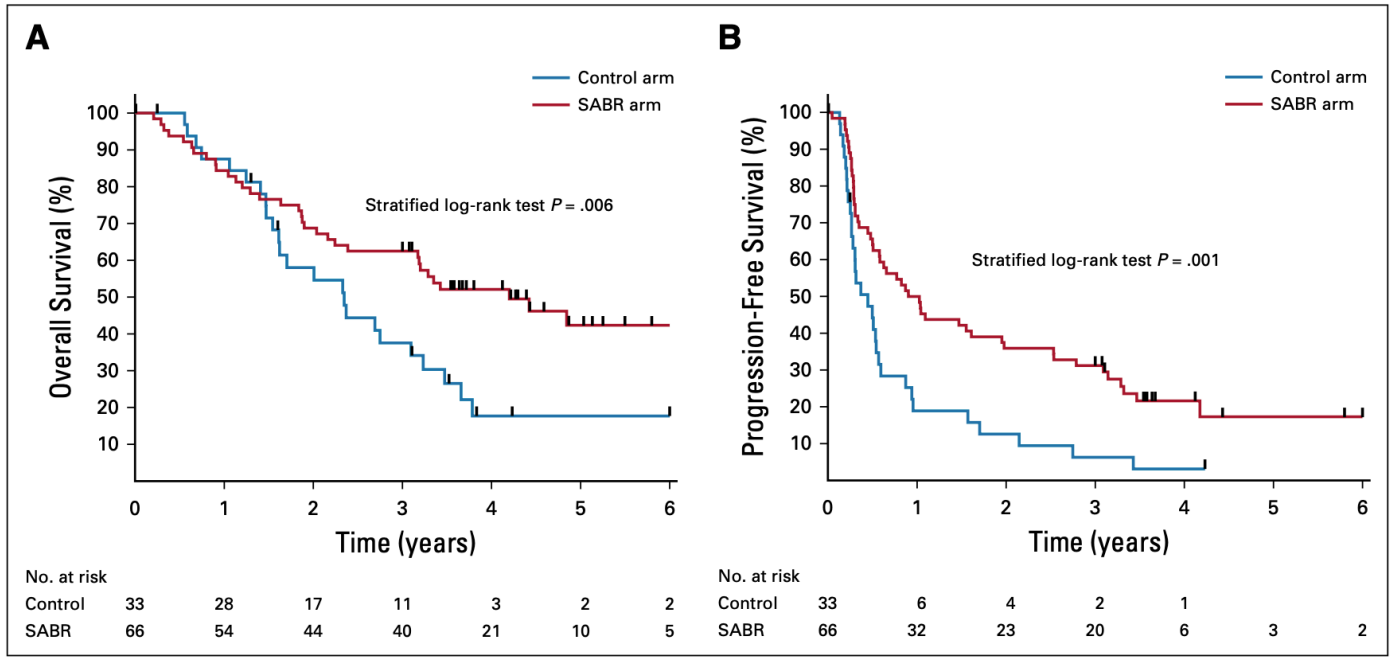


FIG 2. Kaplan-Meier plots for (A) overall survival and (B) progression-free survival. SABR, stereotactic ablative radiotherapy.

- First randomized trial to demonstrate an impact of any ablative therapy on a primary end point of ***overall survival*** in patients with oligometastases

Palma DA, et al. J Clin Oncol (2020) 38:2830-2838

Better median OS with SBRT

- Median OS was 28 months in SOC arm v **50 months** in SBRT arm; stratified log-rank test *P* = .006; **HR, 0.47;** 95% CI, 0.27 to 0.81)
- Median PFS was 5.4 months with SOC and **11.6 months** with SBRT; stratified log-rank test *P* = .001; **HR, 0.48**; 95% CI, 0.31 to 0.76)
  - Overall long-term LC rate: 46% in SOC v **63%** in SBRT (*P*=.039)
  - No differences in long-term analysis of quality-of-life scores over time

COST-EFFECTIVE ANALYSIS OF SABR-COMET

- Assess the cost-effectiveness of SBRT versus SOC in oligometastatic setting (1-5 mets)
  - Developed a Markov model to evaluate the cost-effectiveness of SBRT versus SOC, with the incremental cost-effectiveness ratio (ICER) as the primary outcome
    - Used individual-level data from the trial to derive utilities, event probabilities, and other model parameters
  - Estimated direct medical costs from the Canadian health care system perspective from published literature and adjusted to 2018 CAD
    - Used prespecified willingness-to-pay (WTP) threshold of $100,000 per quality-adjusted life year (QALY)
    - ***SABR was cost-effective at an ICER of $37,157 per QALY gained***
      - Probabilistic sensitivity analysis revealed that SABR was cost-effective in 97% of iterations at a WTP threshold of $100,000 per QALY
  - One important limitation: SABR-COMET was conducted in an era when immunotherapies and targeted therapies were not widely used

Qu XM, et al. IJROBP (2021) 109: 1176-1184

LARGE INTERNATIONAL MULTI-INSTITUTIONAL RETROSPECTIVE CASE SERIES

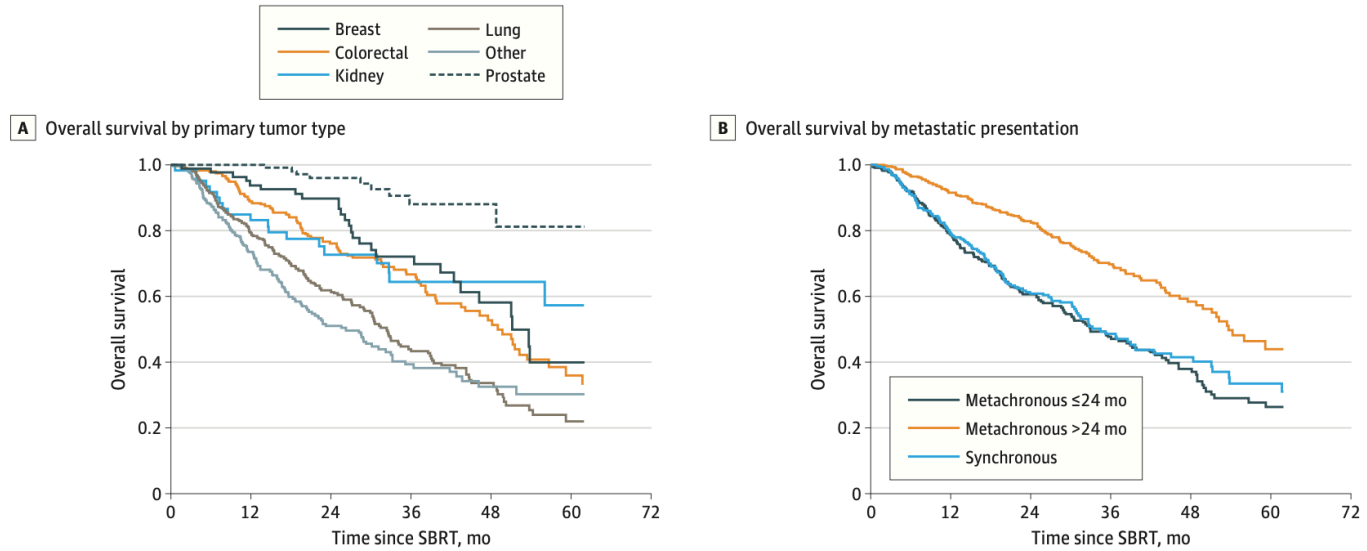
- Pooled collective cases of patients treated with <5 extracranial oligometastasis (OM) whose primary tumor was treated definitively with SBRT
  - Consecutive cases from 2008-2016 from 6 high-volume academic radiation oncology centers
- Primary objective: identify rates of OS

- 1033 treated patients, mean age: 68.0 years
  - Majority (57.7%) had 1 OM, 245 patients (23.7%) had 2 OMs
    - Most common site: lung (n=414) > bone (n=277) > liver (n=124)
  - Median follow-up 24.1 mo
  - Median OS: 44.2 mo (95% CI, 39.2-48.8 months)
    - 1 yr OS: 84.1% (95% CI, 81.7%-86.2%)
    - 2 yrs OS: 69.6% (95% CI, 66.5%-72.5%)
    - 3 yrs OS: 56.7% (95% CI, 53.0%-60.2%)
    - 5 yrs OS: 35.2% (95% CI, 30.1%-40.3%)

Poon I, et al. JAMA Network Open; (2020) 3(11):e2026312.

LARGE INTERNATIONAL MULTI-INSTITUTIONAL RETROSPECTIVE CASE SERIES

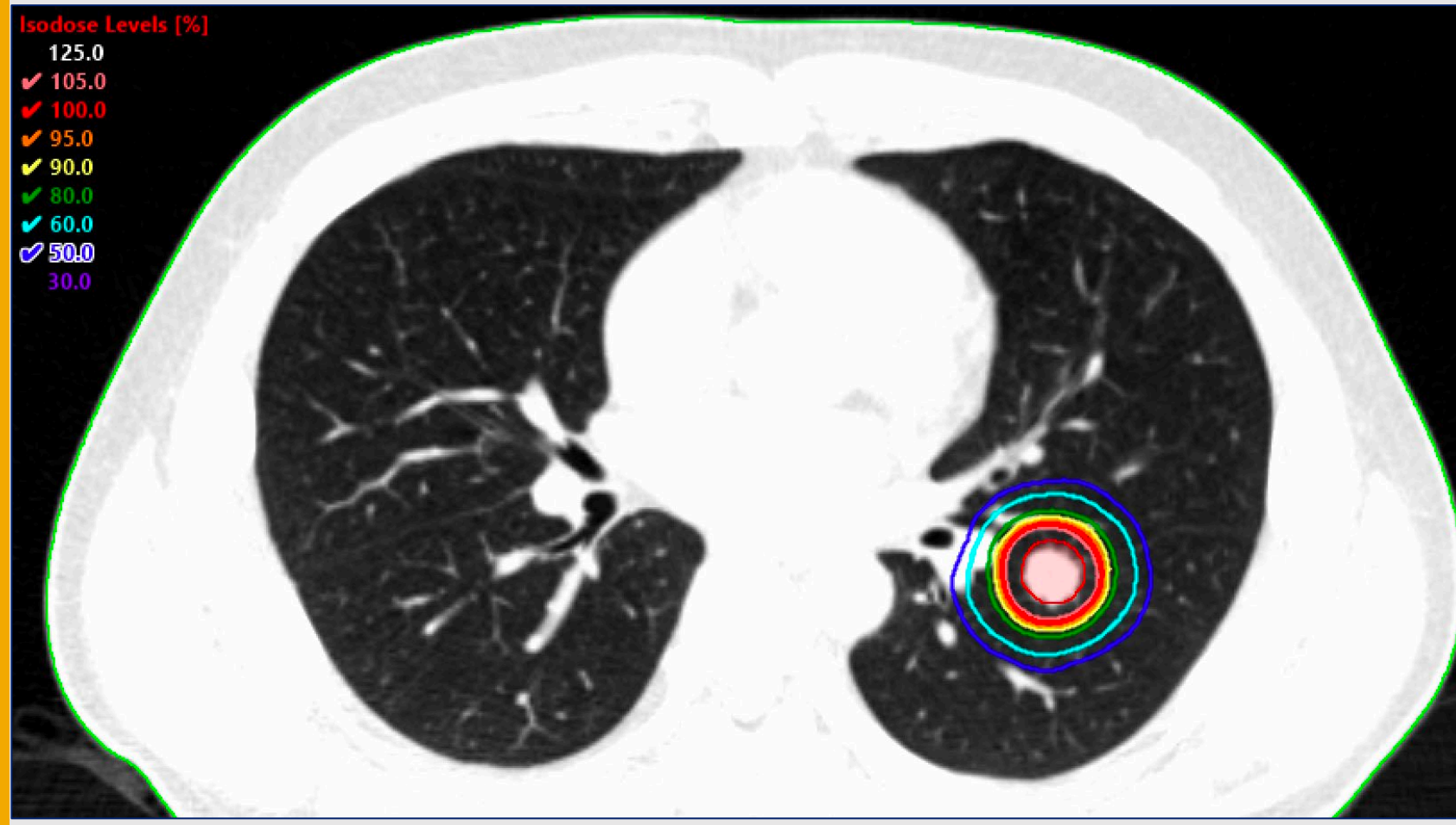
Figure 2. Overall Survival



Poon I, et al. JAMA Network Open; (2020) 3(11):e2026312.

- Overall, favorable long-term OS and wide-spread progression rates
  - Prostate cancer had the longest OS rates
  - Breast cancer pts had median OS of 51 months (95% CI, 42.4-infinity months)
  - Patients who had <u>metachronous disease >24 mo had significantly longer survival</u> compared to <u>≤</u> 24 mo or synchronous presentation

SBRT FOR OLIGOMETASTATIC – BREAST CANCER SPECIFIC



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UNIVERSITY OF ROCHESTER EXPERIENCE

- Long term results of two institutional, prospective pilot trials using SBRT for limited metastatic disease with breast cancer patients separated from nonbreast cancer patients
  - Breast cancer patients had
    - 6-yr OS: 47%
    - 6-yr freedom from DM: 36%
    - 6-year LC: 87%

- Conclusions: “breast cancer patients with ≤5 clinically apparent metastases generally fare well after SBRT to oligometastatic lesions”
  - Encouraging survival and PFS
  - SBRT to asymptomatic lesions could be warranted if select lesions could cause symptoms with further growth

Milano MT, et al. IJROBP (2012) 83:878-886

PHASE II TRIAL IN BREAST CANCER PATIENTS WITH OLIGOMETASTATIC DISEASE

- Prospective multicenter trial to see if radical RT to OM sites could improve PFS from 30% (published literature) to 50% at 2 years
  - Permitted ≤5 mets, primary tumor controlled
    - FDG-PET/CT required
    - No brain mets
  - Could do SBRT (30-45 Gy in 3 fx or 60 Gy IMRT in 25 fx)
    - Systemic therapy was allowed with RT
  - 54 pts and 92 lesions treated from Jan 2012 – Dec 2015
    - 80% HR+, 7% HER+, 13% triple negative
    - 61% received chemotherapy with RT (taxanes or capcitabine in 30 cases)
- Most common site was bone (n=60) > lymph nodes (n=23) > liver (n=5) > lung (n=4)
- Median follow-up of 30 months
  - 1-yr PFS: 75%
  - **2-yr PFS: 53%**
  - 2-yr LC: 97%
  - 2-yr OS: 95%
  - No grade 3+ toxicities
- Conclusions: Patients with OM breast cancer treated with radical RT to all metastatic sites may achieve long-term PFS, without significant treatment-related toxicity

Travo M, et al. Radiother Oncol (2018) 126:177-180

BOSTON TRIAL – MELBOURNE, AUSTRALIA

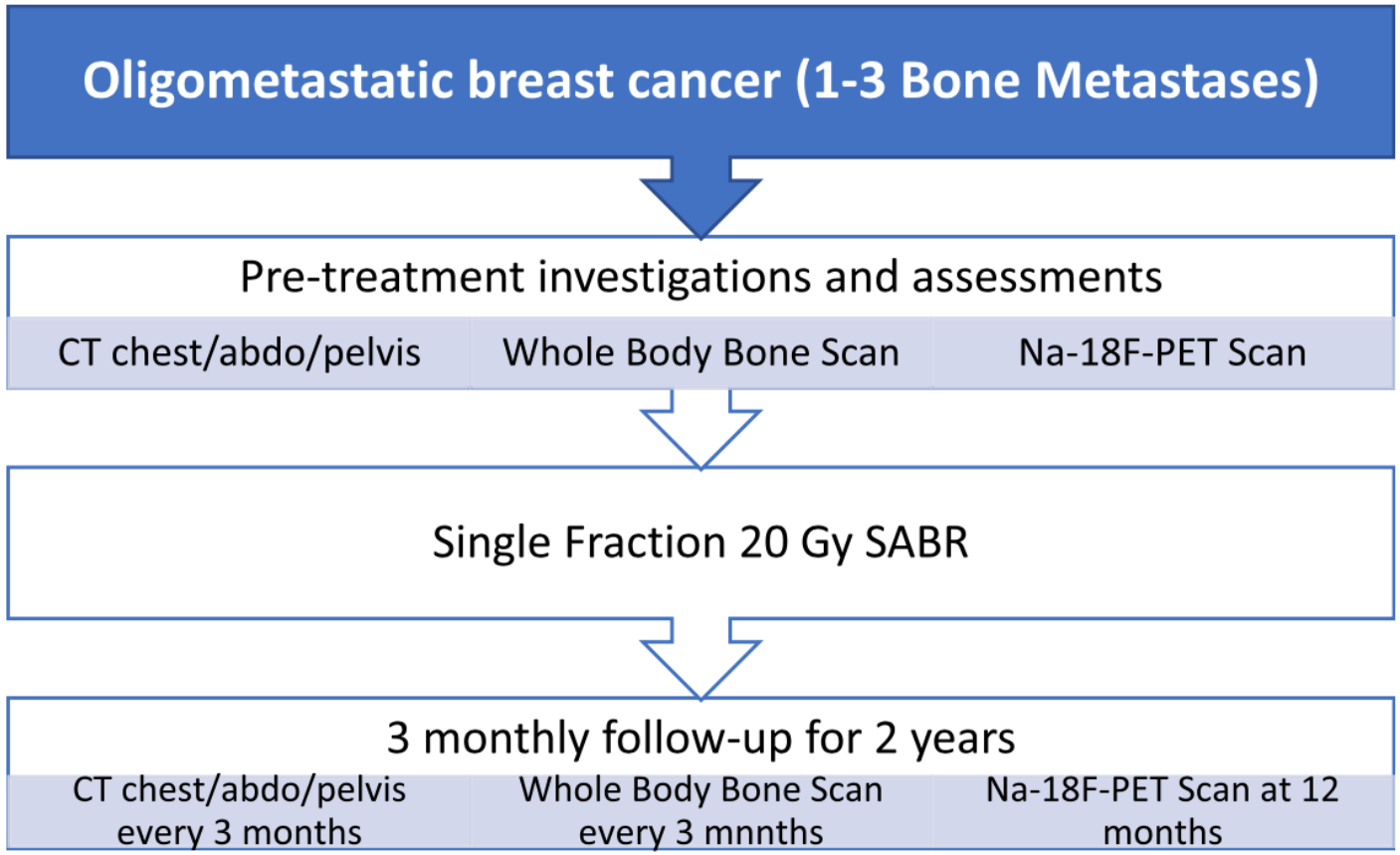

Fig. 1. Study design.

David S, et al. The Breast (2019) 49:55-62

- 'Bone Only STereotactic ablation for Oligometastatic Breast Neoplasia'
- Single institution, prospective study
  - Primary endpoints:
    - Feasibility
    - Tolerability
  - Secondary endpoints:
    - Local and distant progression-free survival
    - Toxicity
    - Response assessment

BOSTON TRIAL

- 15 patients enrolled with 19 oligometastatic lesions treated (mostly bone)
  - Followed for 2 years
  - Median age 63 yo
    - All patients had primary breast cancer resected
    - Majority had hormone receptor positive cancers (86%)
  - Overall feasibility of treatment delivery and image guidance verification of treatment delivery within 5 mm of planned delivery was 80%
  - No grade 3 or 4 toxicities within 24 mo of SBRT
  - 2 yr local PFS: 100%
  - 2 yr distant PFS: 67%

- Conclusions: SBRT is feasible, well-tolerated, and effective in this cohort of bone-only oligometastatic disease

David S, et al. The Breast (2019) 49:55-62

NRG BR002 – PHASE IIR/III TRIAL OF SBRT AND/OR SURGICAL RESECTION FOR NEWLY OLIGOMETASTATIC BREAST CANCER

- Prospective trial randomizing oligometastatic breast cancer patients to SBRT or surgical resection + standard of care systemic therapy (SOC ST) vs SOC ST alone
  - ≤ 4 extracranial mets and on first line SOC ST for ≤ 12 months without progression
    - Max dimension ≤5 cm
  - Stratified by:
    - Mets number (1 vs > 1)
    - ER/PR (+/-)
    - Her2 status (+/-)
    - Chemotherapy use (yes vs no)
  - Variety of SBRT courses permitted (1, 3, or 5 fractions) depending on metastatic site
  - SOC ST was at discretion of treating physician
- Primary objective: to determine whether SBRT/surgical resection provides sufficient signal for improved PFS to warrant phase III trial
  - Phase III primary objective: whether SBRT/surgical resection improves OS

Chmura SJ et al. *J Clin Onc* 40, no. 16_suppl (June 01, 2022) 1007-1007.

NRG BR002

- Hypothesized that metastasis-directed therapy of all visible lesions with systemic therapy would improve PFS (HR 0.55, corresponding to median PFS from 10.5 to 19 months)
- Randomized 125 eligible patients to phase IIR, median age 54 yo
  - Majority were hormone receptor +/HER2- (79%), 13% HER2+, 8% triple negative
- Median f/u 35 mo

- **Similar PFS**
  - 24-mo PFS: 45.7% in SOC ST vs 46.8% in ablation arm
  - 3-yr PFS estimates: 32.8% in SOC ST arm vs 38.1% in ablation arm
  - Median PFS were similar: 23.0 mo in SOC ST arm vs 19.5 mo in ablation arm
  - Very rare high-grade toxicities

- Will not continue to phase III

Chmura SJ et al. *J Clin Onc* 40, no. 16_suppl (June 01, 2022) 1007-1007.

NRG BR002 – POINTS/QUESTIONS TO CONSIDER

- Heavily skewed to HR+/HER2- patients (79%)
  - *Could there be benefit to other subtypes like HER2+ or triple negative?*

- Enrolled at ~initial discovery of metastatic disease, within 365 days of initial disease
  - Allowed for first-line standard therapy to be given prior to study enrollment
    - Restriction: SOC therapy could not be >12 mo
  - *Could there be a benefit in patients who have been on systemic therapy for >12 mo and have had stable disease?*

- Did not stratify for synchronous vs metachronous presentation
  - *Could there be a benefit in those with metachronous disease, particular among those with long duration from initial diagnosis?*

ONGOING RANDOMIZED CLINICAL TRIALS

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METASTASES-DIRECTED RADIOTHERAPY IN ADDITION TO STANDARD SYSTEMIC THERAPY IN PATIENTS WITH OLIGOMETASTATIC BREAST CANCER (OLIGOMA)

Plan for 564 participants
- Stage IV breast cancer with <5 clinical mets
  - Max 3 brain mets
- Local RT to all mets must be possible
- Systemic tx given per national guidelines

Systemic therapy
(no ablative RT)

Systemic therapy + ablative RT to all met sites
- SBRT given in 3-5 fx

Co-primary endpoints:
- Progression-free survival
- QOL (EORTC QLQ-C30) at 12 weeks post randomization

NCT04495309

OPEN to accrual 3/5/2021
- Estimated recruitment duration: 36 mo
- Estimated completion: 2025

Sponsor: University Hospital Schleswig-Holstein

- Recruiting at 50 sites in Germany and Austria

https://clinicaltrials.gov/ct2/show/NCT04495309

CONVENTIONAL CARE VERSUS RADIOABLATION FOR EXTRACRANIAL OLIGOMETASTASES (CORE) TRIAL

Accrued 245 participants
- Stage IV breast, prostate, NSCLC cancer with ≤3 clinical mets
- Local RT to all mets must be possible
- Systemic tx given per national guidelines

Standard of care (SOC), ie:
- Chemotherapy
- Endocrine therapy
- Surgery
- Palliative radiotherapy

SBRT + SOC
- SBRT will precede SOC

Primary endpoint:
- Progression-free survival

Phase II/III. Multi-center, non-blinded randomized controlled trial

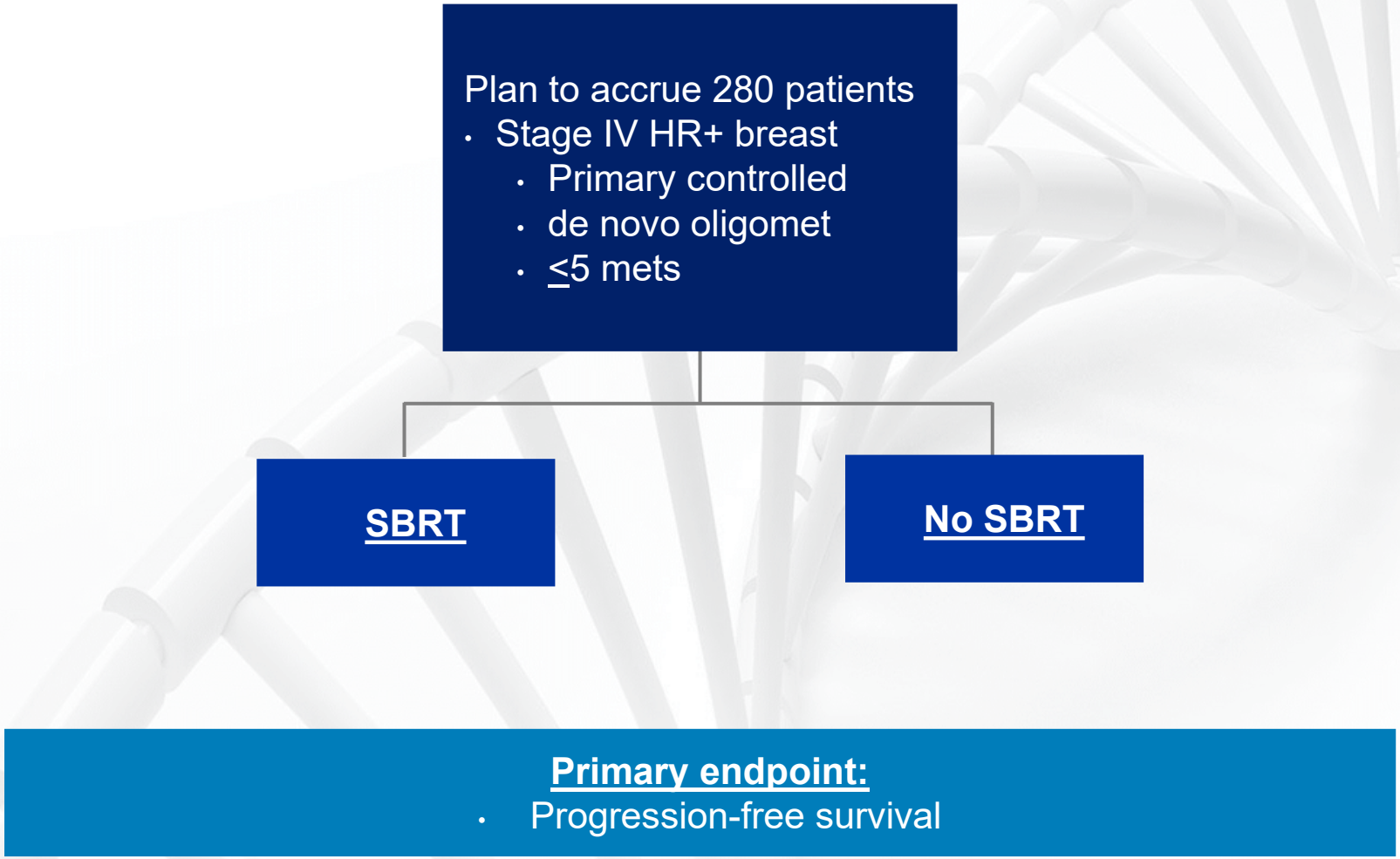
NCT02759783

Active, but not recruiting
- Estimated completion: Oct 2024

Sponsored by Royal Marsden NHS Foundation Trust

https://classic.clinicaltrials.gov/ct2/show/NCT02759783

TRIAL OF SUPERIORITY OF STEREOTACTIC BODY RADIATION THERAPY IN PATIENTS WITH BREAST CANCER (STEREO-SEIN)



Primary endpoint:
- Progression-free survival

Phase III trial

NCT02089100

Recruiting, but also noted unknown as of July 2018 post
- Estimated completion Feb 2023

Sponsored by Gustave Roussy, Cancer Campus, Grand Paris

https://classic.clinicaltrials.gov/ct2/show/NCT02089100

A TRIAL EVALUATING THE EFFICACY OF METASTASECTOMY IN PATIENTS WITH OLIGO-METASTATIC BREAST CANCER (OMIT)

Plan to accrue 172 patients
- Stage IV breast ≤3 clinical mets
  - Only allow:
    - Central lung lesions
    - Peripheral lung lesions
    - Liver metastases
- No local recurrence at primary site

Standard of care (SOC), ie:
- Chemotherapy
- Endocrine therapy
- Surgery
- Palliative radiotherapy

Mestatectomy → SOC
- Surgical resection of metastatic site prior to SOC

Primary endpoint:
- Overall survival

NCT04413409

Recruiting, opened in 2019
- Estimated completion: Mar 2025

Sponsored by Fudan University

https://classic.clinicaltrials.gov/ct2/show/NCT04413409

RADIOTHERAPY FOR EXTRACRANIAL OLIGOMETASTATIC BREAST CANCER

Plan to accrue 170 patients
- Stage IV HR+ breast
  - Primary controlled
  - de novo or metachronous
  - ≤5 mets

Standard of care (SOC), ie:
- Chemotherapy
- Endocrine therapy
- Targeted therapy
- Immunotherapy

RT + SOC
- SBRT preferred, but conventional RT allowed

Primary endpoint:
- Progression-free survival

Phase III trial

NCT04646564

Recruiting as of Jan 2022 post
- Estimated completion April 2026

Sponsored by Cancer Institute and Hospital, Chinese Academy of Medical Sciences

https://classic.clinicaltrials.gov/ct2/show/NCT04646564

LOGISTICS OF SBRT

Example of abdominal compression to limit respiratory motion

Sen CA. Contemp Oncol (Pozn) 2022; 26 (2): 133–138

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TIMELINE FOR SBRT

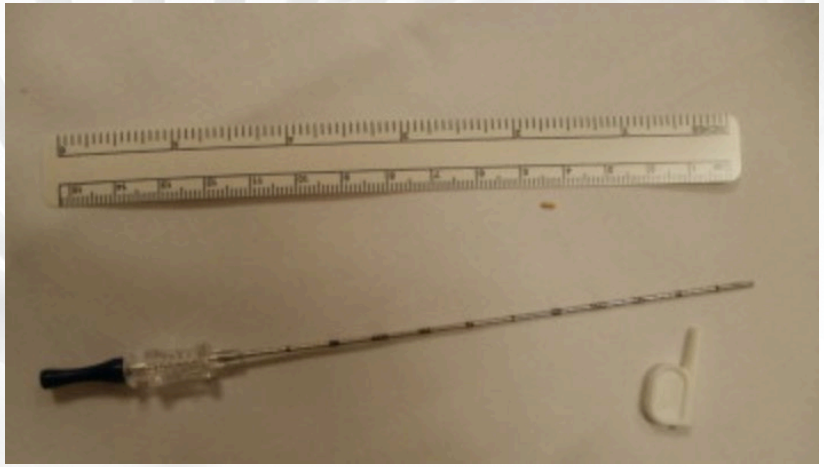
Helpful Diagnostic Imaging

- PET/CT
- MRI
  - Important for liver and spine mets
    - *Not* feasible if there is epidural extension to cord

Fiducial Placement (optional)

- 2-3 gold markers placed around the tumor
  - Liver
  - Lung
- Needs to be done *before* simulation scan

Oldrin G, et al. Diagnostic and Interventional Imaging 2015;96:589-592



Consult with Rad Onc

- Gather H&P
- Discuss risks and benefits of SBRT
- Review logistics/timing
- Can refer to Interventional Radiology for fiducial placement

RT Simulation Scan

- Position patient
- Limit respiratory motion (if applicable)
- Plan treatment (~1.5 wk)
  - Can fuse diagnostic images with planning CT scan

Treatment (~1.5 wk after simulation)

- Cone-beam CT scan prior to treatment
  - Overlay with planning CT scan
- Can use fiducial tracking (if applicable)

KEY TAKEAWAYS FOR TREATING OLIGOMETASTATIC DISEASE WITH SBRT

- **Several retrospective, phase I and II studies have demonstrated high rates of local control and low toxicity with SBRT in well-selected patients with oligometastatic breast cancer**
  - Encouraging survival and PFS
  - Very few cases of severe adverse events
  - No phase III data available yet, but multiple trials are accruing or recently completed accrual
  - Dose and fractionation can vary depending on size, location, chemo schedule, etc
    - Coordinate with rad onc team regarding logistics of SBRT since SBRT requires time to plan and deliver optimal treatment

Conclusions:

- SBRT is an effective, non-invasive treatment option with good local control & toxicity profile
- Select patients with limited metastases may be ideal candidates for SBRT
- Additional data from randomized trials are pending

Thank you for your attention!