RADIATION RISK VERSUS PROJECTED CLINICAL BENEFIT OF SURVEILLANCE IMAGING FOR EARLY DETECTION AND TREATMENT OF BREAST CANCER METASTASES

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I. INTRODUCTION

- In 2017, over 252,000 women in the United States will be diagnosed with invasive breast cancer.[1]
- Approximately 11% (26,000) of these women will develop distant metastatic breast cancer (MBC) after an initial M0 diagnosis[2] and will account for nearly 2/3 of the 40,610 breast cancer deaths that occur annually.[1,3]
- Currently, MBC is associated with a 20% overall survival (OS) and 2% disease-free survival (DFS) at 5 years.
- Oligometastases = only a few (<7) small (< 5 cm) observable metastases that are amenable to surgery or SBRT.
- Numerous studies have achieved favorable OS and DFS for oligoMBC treated using combined systemic + local therapy.
- Current NCCN guidelines for asymptomatic breast cancer survivors omit proactive imaging for the detection of early-stage metastatic disease, regardless of a patient's metastatic risk, based upon data from a 1987-1993 study.
- 85% of patients with MBC were diagnosed because of presentation of clinical symptoms, and 81.7% of these had > 5 sites of metastases at presentation.[4]
- In the absence of surveillance imaging, MBC is typically advanced, with multiple tumor masses afflicting multiple organs.

HYPOTHESIS: Proactive imaging for detection of early-stage MBC in high-risk patients will achieve improved OS & DFS.

OBJECTIVES: To (1) describe the imaging parameters needed to achieve the goal of identifying MBC at an early stage for definitive surgical or radiosurgical treatment; (2) estimate the radiation risks associated with the repeated body imaging under the required protocol; and (3) estimate the anticipated survival benefit for high-risk patients under this protocol.

II. PROPOSED IMAGING METHODOLOGY

IMAGING MODALITIES

- Contrast-enhanced MRI of the brain, diagnostic-quality CT and PET of all other organs, as per ACR recommendations.

SCAN INTERVAL

- Goal: select the longest interval such that after initial detection, a suspicious nodule will remain <15 mm at next follow-up.
- Minimum nodule size for diagnosis in CT is 5 mm.
- Expected MBC nodule doubling time is 1.7 months.[5]
- Optimal interval is 9 months (Table 1).

Table 1. Size of a nodule (in mm) as a function of scan interval (in months; along columns) and scan number (along rows) for a metastasis of diameter 4 mm at time zero and a doubling time of 1.7 months.

	Scan interval		
Tumor diameter (mm)	6 months	9 months	12 months
Scan #1	6.6	7.4	8
Scan #2	11.0	13.6	16.1
Scan #3	18.1	25.2	32.2
Scan #4	30.0	46.5	64.6

SCAN INITIATION

- Goal: select longest delay where MBC is < 5 mm.
- Average time to first symptomatic MBC is 5.3 years.[6]
- Symptomatic MBC detected most frequently in year 2, followed by years 3, 1, & 4.[6]
- Symptomatic nodule size ~15 – 30 mm.
- Expected MBC nodule doubling time is 1.7 months.[5]
- Imaging detection will precede symptoms by 2+ years.
- Optimal time to first scan is also 9 months.

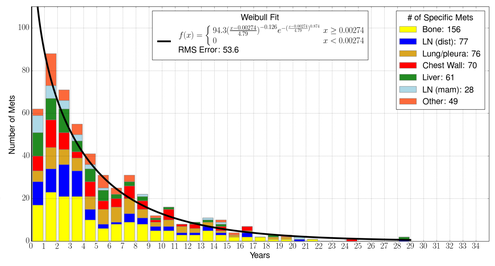

Figure 1. Presentation of MBC over time [in years] to various target organs, from Newton, *et al.*[6]

SURVEILLANCE DURATION

- Goal: select shortest follow-up duration to capture 75+% of MBC.
- 85% of MBCs are diagnosed because of clinical symptoms.
- Symptomatic MBC detected most frequently in years 1-6.[6]
- Imaging detection precedes symptomatic detection by 2+ years.
- Optimal duration of surveillance is ~4 years.

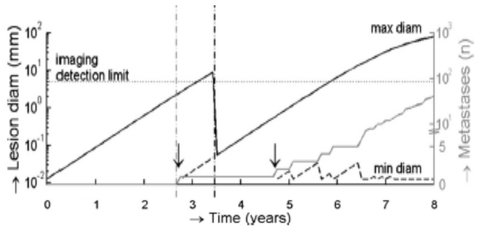

Figure 2. Model-predicted initiation, growth, initial presentation, and spawning of MBC over time [in years], from Coumans *et al.*[5]

OPTIMAL SURVEILLANCE IMANGING PROTOCOL

- MRI of brain, and whole-body PET/CT with diagnostic-quality CT.
- Initial surveillance scan at 9 months post-RT.
- Repeat scans every 9 months, out to 45 months (3.75 years) post-RT.
- Total of 5 PET/CT scans over 3 years.

III. RADIATION EXPOSURE CALCULATION

- PET scan exposure: 6.23 mSv.
- Whole-body diagnostic CT (C3 vertebra in neck to mid-thigh): 12 mSv.
- Cumulative exposure over 5 scans: **91.15 mSv**.
- Average yearly background radiation: 3.1 mSv.
- 5-year occupational dose limit for health care workers: 100 mSv.
- Average dose to the lung during breast cancer radiotherapy: ~9,800 mSv.
- Lifetime attributable risk (LAR) of cancer incidence for 40+ year old woman with one-time 91 mSv exposure: 0.78%.[7]
- Increased lifetime risk of cancer mortality (LRCM) for a 45-year-old woman exposed to 91 mSv: 0.074%.[8]

(Tables 2-4 of BEIR-V[8] give 0.081% LRCM for 100 mSv exposure; scaled here by 91/100)

IV. PROJECTED SURVIVAL BENEFIT CALCULATION

METASTATIC BREAST CANCER RISK

- Risk of MBC for the selected high-risk population: 30%

FIVE-YEAR OVERALL SURVIVAL STATISTICS

- All MBC: 20%
- Oligo-MBC: 48.5%[4,9]
- Non-oligo MBC: 10.7%[4]

INCIDENCE OF OLIGO-MBC

- Currently (absent surveillance imaging): 22%[4]
- Under surveillance imaging (est.): > 60%

Table 2. Comparison of image-based screening and surveillance studies with scan-induced cancer risk versus benefit.

	Cancer incidence, all subjects	Cancer mortality, all subjects	Mortality decrease with screening	# subjects to prevent 1 death	# of scans per subject / dose per scan [mSv]	LAR cancer mortality per 100k
National Lung Screening Trial	4.0%	1.7%	0.33%	320	3 / 1.5	24 (41)
Mammography for primary breast cancer	12.4%[1]	2.7%[1]	0.4%	2,512 over first 10 years	>10 / 0.3	20-25
Proposed MBC surveillance	>30%	>20%*	3.75%	27	5 / 18.2	740

OVERALL 5-YEAR SURVIVAL OF HIGH-RISK POPULATION

- Assuming 100% survival of the 70% of subjects who do not develop MBC
- Currently (absent surveillance imaging):

$$70\% * 100\% + 30\% * 20\% = 76\%$$

- Under surveillance imaging (est.):
- 60% of the 30% of those who develop MBC (=18% overall) will experience 48.5% 5-year OS
- The remaining 40% of the 30% (=12% overall) will experience 10.7% 5-year OS

$$70\% * 100\% + 18\% * 48.5\% + 12\% * 10.7\% = 80.01\%$$

- 5-year survival benefit: 4.0%
- Benefit/risk ratio: $\frac{4.0}{0.074} = 54.1$
- If 1,351 patients received surveillance scans under this protocol, 1 would be expected to die from cancer sometime during her lifetime due to the scans, while 54 would be alive at 5 years who otherwise would have died from MBC.

V. CONCLUSIONS AND DISCUSSION POINTS

We found a 54:1 survival benefit-to-radiation mortality risk ratio for adding surveillance whole-body imaging for detection and treatment of early metastases in breast cancer survivors with a 30% risk for developing distant metastases.

- Any breast cancer patient with a metastatic risk higher than 0.55% would benefit from this surveillance imaging protocol, including stage I survivors (with an 8% risk).

DISCUSSION POINTS

- The optimal imaging duration and intervals may differ for different BC sub-types (up to 10 years for luminal A[10]).
- Cancer risk and death estimates are based on data from healthy individuals, and may differ for cancer survivors due both to patients' genetic and environmental predispositions, and prior damage from chemotherapy and radiation treatment.
- None of the prior oligo-MBC treatment studies were part of a controlled clinical trial, thus survival benefit is unproven.
- More accurate survival estimates for oligo-MBC will become available upon completion of NRG-BR002 in 2022.
- Prior outcome studies were without the benefit of surveillance imaging to find and treat MBC at the earliest stage; thus, long-term survival may be yet further improved over the previous findings.
- We recommend evaluating the benefit of surveillance imaging to standard of care follow-up in a prospective study.

V. REFERENCES

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