Clinical and Molecular Markers of Long-Term Survival After Oligometastasis-Directed Stereotactic Body Radiotherapy (SBRT)

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BACKGROUND: The selection of patients for oligometastasis-directed ablative therapy remains a challenge. The authors report on clinical and molecular predictors of survival from a stereotactic body radiotherapy (SBRT) dose-escalation trial for oligometastases.

METHODS: Patients who had from 1 to 5 metastases, a life expectancy of >3 months, and a Karnofsky performance status of 60 received escalating SBRT doses to all known cancer sites. Time to progression, progression-free survival, and overall survival (OS) were calculated at the completion of SBRT, and clinical predictors of OS were modeled. Primary tumor microRNA expression was analyzed to identify molecular predictors of OS. RESULTS: Sixty-one evaluable patients were enrolled from 2004 to 2009. The median follow-up was 2.3 years for all patients (range, 0.2-9.3 years) and 6.8 years for survivors (range, 2.0-9.3 years). The median, 2-year, and 5-year estimated OS were 2.4 years, 57%, and 32%, respectively. The rate of progression after SBRT was associated with an increased risk of death (hazard ratio [HR], 1.44; 95% confidence interval [CI], 1.24-1.82). The time from initial cancer diagnosis to metastasis (HR, 0.98; 95% CI, 0.98-0.99), the time from metastasis to SBRT (HR, 0.98; 95% CI, 0.98-0.99), and breast cancer histology (HR, 0.12; 95% CI, 0.07-0.37) were significant predictors of OS. In an exploratory analysis, a candidate classifier using expression levels of 3 microRNAs (miR-23b, miR-449a, and miR-449b) predicted survival among 17 patients who had primary tumor microRNA expression data available.

CONCLUSIONS: A subset of oligometastatic patients achieves long-term survival after metastasis-directed SBRT. Clinical features and primary tumor microRNA expression profiling, if validated in an independent dataset, may help select oligometastatic patients most likely to benefit from metastasis-directed therapy. Cancer 2016;122:2242-50. © 2016 American Cancer Society.

KEYWORDS: oligometastases, stereotactic body radiotherapy, microRNA, biomarker, classifier.

INTRODUCTION

Since the proposal of the oligometastatic state,1 defined as an intermediate state between locoregionally confined cancer and widespread metastases, multiple nonrandomized trials have reported long-term disease control after extracranial oligometastasis-directed therapy. Early experiences involving surgical resection of lung and liver oligometastases demonstrated that overall survival (OS) rates of approximately 35% to 50% at 5 years and 20% to 25% at 10 years could be achieved in appropriately selected patients.2-5

The development of ablative stereotactic body radiotherapy (SBRT) has enabled potentially curative, metastasis-directed therapy for non-surgical candidates. SBRT and surgery provide comparable treated metastasis control (TMC) and OS rates.6-13 However, appropriate patient selection, optimal treatment modality, and the long-term benefit from curative-intent interventions of any modality in patients with oligometastases have yet to be established.14

We previously reported outcomes of the first prospective, multiorgan oligometastasis-directed SBRT dose-escalation trial with a median follow-up of 2.6 years for survivors.15 Here, we report outcomes with a median follow-up of 6.8 years for survivors, and we model clinical features associated with long-term survival. In addition, we characterize primary
tumor microRNA expression patterns correlated with survival. From this, we derive a candidate 3-microRNA classifier that may identify patients with oligometastases who have a better prognosis and are more likely to benefit from metastasis-directed therapy.

MATERIALS AND METHODS

Patients

Patients with pathologically confirmed, American Joint Committee on Cancer (sixth edition) stage IV cancer (any histology) who had 1 to 5 malignant sites on standard radiographic and metabolic imaging were eligible for this prospective radiation dose-escalation study (Table 1). Eligibility criteria have been previously described.15 Each metastasis had to be ≤10 cm or ≤500 mL in volume on standard imaging, and no previous radiotherapy to treated metastases was allowed. Patients could not receive systemic cytotoxic chemotherapy during SBRT; hormone therapy was allowed. Adjuvant and salvage therapies were left to the discretion of the treating physicians.

Informed consent was obtained before protocol treatment. The University of Chicago Institutional Review Board approved the study (approval no. 136198B).

Treatment and Endpoints

Details of radiation treatment planning and delivery have been previously described.15 A 3 × 3 dose-escalation schema was used with cohorts for each anatomic site escalated in 6 gray (Gy) increments (2 Gy per fraction). The starting dose for all sites was 24 Gy, and the ceiling for all cohorts was 60 Gy in 3 fractions; however, the trial closed with the 48 Gy cohort, before reaching the maximum tolerated dose. In general, the radiation dose was prescribed to the planning target volume edge, typically to the 80% to 90% isodose line, with 95% of the planning target volume required to receive 95% of the planned dose.

The primary endpoint was determination of the maximum tolerated dose and dose-limiting toxicity (defined as grade 4-5 hematologic toxicity or grade 3-5 nonhematologic toxicity, excluding nausea, vomiting, and alopecia) of SBRT for each of 5 anatomically defined cohorts: head and neck, lung, liver, abdomen, and extremities. The secondary endpoints were response rate, OS, progression-free survival (PFS), and patterns of failure.

Follow-Up

Patients returned every 2 weeks for 1 month, monthly for 3 months, and quarterly thereafter. Acute toxicities were scored according to the Common Terminology Criteria for Adverse Events (version 3.0.16).16 Late toxicities were scored according to the Radiation Therapy Oncology Group late toxicity scoring system.17 Each metastasis was a target lesion that was independently assessed for response. Patterns of progression were determined by assessing all treated metastases and untreated tumors (primary tumors and metastases) on all follow-up studies.

Differential MicroRNA Expression Analysis

MicroRNA expression profiles of 17 primary tumor samples obtained from patients treated on protocol were analyzed with the TaqMan MicroRNA Array A Card v2.0, as

### Table 1. Patient and Tumor Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients</th>
<th>No. of Months</th>
<th>%</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary sites (histology)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>7</td>
<td></td>
<td>11.5</td>
<td></td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>6</td>
<td></td>
<td>9.8</td>
<td></td>
</tr>
<tr>
<td>Head and neck squamous cell</td>
<td>5</td>
<td></td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>Nonsmall cell lung</td>
<td>11</td>
<td></td>
<td>18</td>
<td></td>
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<tr>
<td>Renal</td>
<td>8</td>
<td></td>
<td>13.1</td>
<td></td>
</tr>
<tr>
<td>Sarcoma</td>
<td>5</td>
<td></td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>Small cell lung</td>
<td>5</td>
<td></td>
<td>8.2</td>
<td></td>
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<tr>
<td>Other (gallbladder, ovary, skin, thy-</td>
<td>14</td>
<td></td>
<td>23</td>
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<tr>
<td>mus, thyroid, parotid, PNET)</td>
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<tr>
<td>Induced oligometastases</td>
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<td></td>
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<tr>
<td>Yes</td>
<td>8</td>
<td></td>
<td>13.1</td>
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</tr>
<tr>
<td>No</td>
<td>53</td>
<td></td>
<td>86.9</td>
<td></td>
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<tr>
<td>Oligometastases per patient:</td>
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<tr>
<td>No. treated on protocol</td>
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<tr>
<td>1</td>
<td>33</td>
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<td>54.1</td>
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<tr>
<td>2</td>
<td>12</td>
<td></td>
<td>19.7</td>
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<tr>
<td>&gt;3</td>
<td>16</td>
<td></td>
<td>26.2</td>
<td></td>
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<tr>
<td>Distant metastasis-free interval, mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0 (metastatic at initial diagnosis)</td>
<td>7</td>
<td></td>
<td>11.5</td>
<td></td>
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<tr>
<td>0-3</td>
<td>12</td>
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<td>3-6</td>
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<td>6-12</td>
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<td>13.1</td>
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<tr>
<td>12-24</td>
<td>5</td>
<td></td>
<td>8.2</td>
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<tr>
<td>24-48</td>
<td>11</td>
<td></td>
<td>18</td>
<td></td>
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<tr>
<td>&gt;48</td>
<td>13</td>
<td></td>
<td>21.3</td>
<td></td>
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<tr>
<td>Median</td>
<td>[11.6]</td>
<td>[9.9]</td>
<td>[0-302]</td>
<td>[1-86]</td>
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<tr>
<td>Time from metastasis to SBRT, mo</td>
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<td></td>
<td></td>
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<tr>
<td>0-3</td>
<td>15</td>
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<td>24.6</td>
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<td>4</td>
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<td>24-48</td>
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<tr>
<td>&gt;48</td>
<td>4</td>
<td></td>
<td>6.6</td>
<td></td>
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<tr>
<td>Median</td>
<td>[9.9]</td>
<td>[9.9]</td>
<td>[1-86]</td>
<td></td>
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<tr>
<td>Time to progression after SBRT, mo</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>0-3</td>
<td>20</td>
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<td>32.8</td>
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<tr>
<td>&gt;48</td>
<td>1</td>
<td></td>
<td>1.6</td>
<td></td>
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<tr>
<td>Never progressed</td>
<td>7</td>
<td></td>
<td>11.5</td>
<td></td>
</tr>
<tr>
<td>Median among progressors</td>
<td>[4.3]</td>
<td>[4.3]</td>
<td>[1-64]</td>
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</tbody>
</table>

Abbreviations: PNET, primitive neuroectodermal tumor; SBRT, stereotactic body radiotherapy.
previously described.\textsuperscript{18} The array results are included in a database deposited in the National Center for Biotechnology Information Gene Expression Omnibus and are accessible through Gene Expression Omnibus series accession number GSE25552. Statistical analyses are performed using R Statistical Software (version 3.2.0).\textsuperscript{19} With the “limma” package in R,\textsuperscript{20} linear regression was used to model microRNA expression in tumor samples derived from patients who survived for >3 years and those who did not. Differentially expressed microRNAs were initially identified by nonadjusted $P < .05$ and then were compared using $t$ tests with a Benjamini-Hochberg adjustment for the false-discovery rate.\textsuperscript{21} We used the “glmnet” package in R\textsuperscript{22} to apply elastic net regression ($\alpha = .7$) to normalized microRNA cycle threshold (C\textsubscript{T}) values to select a subset of microRNAs that were associated with OS. A score for predicting survival time was calculated using the coefficients obtained in elastic net regression.

**Statistical Analysis**

We defined treated metastases as controlled if all protocol-treated metastases in a patient demonstrated no evidence of progression from the time of SBRT. Patients who died without progression at any treated metastasis were censored at time of death. We used the Kaplan-Meier method to estimate PFS using the time from SBRT to either death or progression and to estimate OS using the time from SBRT to death.

Rates of progression were determined for each time interval between consecutive scans for each patient. Multiple progression-free scans within any given 6-month interval were considered redundant. Rates were calculated as the number of new metastases or progression events in previously controlled metastases divided by the interval (in years) between nonredundant scans. Individual relations between OS and each binary or continuous candidate predictor variable were examined using Cox proportional-hazards regression.

We performed univariable and multivariable analysis to establish predictors of long-term OS. We also developed a joint longitudinal-survival model to examine the association between OS and the rate of progression after SBRT.\textsuperscript{23} Significant independent predictors of OS were included in this model, and the rate of progression was included as a time-varying covariate. To handle indeterminate metastasis counts, hazard ratios (HRs) were obtained by averaging over possible values from 1000 imputation data sets, replacing each censored count with random draws between the minimum number of new metastases observed and a ceiling of 10. After fitting the joint longitudinal-survival model in each imputation data set, we recorded the HR for the associations between OS and each predictor variable. The 1000 HR estimates for each parameter were used to obtain point estimates (the median HR in each parameter estimate distribution) and 95% confidence intervals (CIs) (2.5% and 97.5% quantiles).

**RESULTS**

**Patients**

Patients were enrolled from November 2004 to November 2009. Of 62 enrollees, 61 patients with 113 metastases were eligible for analysis; 1 patient with recurrent, nonmetastatic disease was considered ineligible. The median follow-up was 2.3 years for all patients (range, 0.2-9.3 years) and 6.8 years for survivors (range, 2.0-9.3 years). Patient and tumor characteristics are provided in Table 1. The median time to first metastasis from initial cancer diagnosis was 11.6 months (range, 0-302 months). The median time from metastatic diagnosis to the end of SBRT was 9.9 months (range, 0.8-302 months). The mean number of protocol-treated metastases per patient was 2, and 27 patients (45%) received treatment to multiple sites.

**Toxicity**

Acute toxicity for this cohort was previously reported.\textsuperscript{15} Only 2 patients experienced grade 3 acute toxicity: 1 patient in the 30 Gy liver cohort experienced grade 3 vomiting, and 1 patient in the 42 Gy lung cohort experienced grade 3 fatigue. There were no grade 4 acute toxicities. Six episodes of grade 3 late toxicity were described in the previous update of this cohort. Since then, there were no additional episodes of grade $\geq$3 toxicity.

**Patterns of Progression and TMC**

Seven patients (11.5%) never progressed after protocol therapy. In another 7 patients (11.5%), first progression occurred only in treated metastases; 4 of those patients received relatively low SBRT doses of 24 or 30 Gy as part of the dose-escalation protocol. Thirty-eight patients (62.3%) had initial progression only outside of protocol-treated metastases. Nine patients (14.8%) progressed initially at both treated and untreated sites.

The median, 2-year, and 5-year Kaplan-Meier estimates of TMC were 2.4 years, 51%, and 44%, respectively. In patients who received a minimum dose of 36 Gy to all protocol-treated metastases, the median, 2-year, and 5-year TMC estimates were 5.7 years, 75%, and 69%, respectively, compared with 1 year, 31%, and
25%, respectively, for patients who received lower doses ($P = .002$) (Fig. 1A). We also investigated disease control in each primary tumor subgroup that included at least 5 patients (Fig. 2A) but observed no statistically significant impact on TMC for any histology, including breast cancer (Fig. 1B).
At last follow-up, 7 patients (11.5%) had no evidence of active cancer, and 3 patients who initially experienced progression at both protocol-treated metastases and elsewhere were controlled with stable disease. The remaining 51 patients had progressive disease: 2 patients (3.3%) progressed only at protocol-treated metastases, 26 patients (42.6%) were controlled at treated metastases but progressed elsewhere, and 23 patients (37.7%) progressed at both protocol-treated metastases and elsewhere.

Kaplan-Meier estimates of the median, 2-year, and 5-year PFS were 5.3 months, 22%, and 12%, respectively. Patients who received ≥36 Gy had a median, 2-year, and 5-year PFS of 9.2 months, 28%, and 20%, respectively, compared with 4.1 months, 15%, and 6%, respectively, in the lower dose cohorts \( (P = .074) \) (Fig. 1C). Patients who had breast cancer had a median, 2-year, and 5-year PFS of 2 years, 57%, and 29%, respectively, compared with 4.7 months, 18%, and 10%, respectively, for patients who had nonbreast cancer \( (P = .054) \) (Fig. 1D). Patients who had small cell lung cancer (SCLC) and sarcoma had an inferior median PFS of 1.9 months \( (P = .016) \) and 1.1 months \( (P = .002) \), respectively, and both groups had a 2-year PFS rate of 0%. No other histologic subgroup had a significant advantage or disadvantage in PFS (Fig. 2B).

OS
At last follow-up, there were 13 survivors (21.3%). Six of those 13 long-term survivors never progressed, 3 progressed outside of treated metastases, 2 progressed at both treated and new metastases but had controlled disease at last follow-up, and 2 progressed at both treated and new metastases, with further progression at last follow-up.

Kaplan-Meier estimates of the median, 2-year, and 5-year OS were 2.4 years, 57%, and 32%, respectively. The SBRT dose had no effect on OS (Fig. 1E). For patients

Figure 2. Kaplan-Meier estimates of (A) treated metastasis control, (B) progression-free survival, and (C) overall survival are illustrated for histologic subgroups that included at least 5 patients. HNSCC indicates head and neck squamous cell carcinoma; NSCLC, nonsmall cell lung cancer; SCLC, small cell lung cancer.

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Kaplan-Meier estimates of the median, 2-year, and 5-year OS were 2.4 years, 57%, and 32%, respectively. The SBRT dose had no effect on OS (Fig. 1E). For patients
with breast cancer, the median, 2-year, and 5-year OS estimates were 4.3 years, 100%, and 50%, respectively, compared with 2 years, 52%, and 29%, respectively, for patients with nonbreast cancer \( (P = .026) \) (Fig. 1F). Patients with SCLC had a median and 2-year OS of 1.1 year and 0% \( (P = .004) \), respectively, and those with NSCLC had a median, 2-year, and 5-year OS of 1.3 years, 36%, and 18% \( (P = .07) \), respectively (Fig. 2C).

On unadjusted Cox regression analysis, a longer time from initial to metastatic diagnosis, a longer time from metastatic diagnosis to the end of SBRT, a longer time to progression after SBRT, and breast cancer histology were significantly associated with a decreased risk of death; whereas an increased rate of progression after SBRT was associated with an increased risk of death (Table 2). Age, solitary oligometastasis, induced oligometastatic state, SBRT dose <36 Gy/3 fractions, and progression at any protocol-treated metastasis were not significantly associated with survival. On multivariable regression analysis, a joint longitudinal-survival model demonstrated an increased risk of death with an increased rate of progression (HR, 1.44; 95% CI, 1.24-1.82). Conversely, breast cancer histology (HR, 0.12; 95% CI, 0.07-0.37), a longer distant metastasis-free interval (HR, 0.98; 95% CI, 0.98-0.99), and a longer time from metastatic diagnosis to the end of SBRT (HR, 0.98; 95% CI, 0.98-0.99) reduced the risk of death (Table 2).

**Prognostic MicroRNA Classifier**

Samples of primary tumor tissue from 17 patients were available for microRNA expression analysis, and primary tissue was unavailable for the remaining 44 patients. It is noteworthy that 12 different histologies were represented among these 17 primary tumors, and only 1 patient in this subset had breast cancer, thus reducing the probability that microRNA analysis would be biased by histology. These 17 patients were broadly representative of the overall cohort. The median age, distant metastasis-free interval, and time from metastatic diagnosis to SBRT were 64.4 years, 16.6 months, and 8 months, respectively, compared with 60.3 years, 11.6 months, and 9.9 months, respectively, for all patients. The mean number of protocol-treated metastases was 1.9 compared with 2.0, and the mean survival time after SBRT was 3.8 years compared with 3.3 years.

The 17 patients for microRNA analysis were divided into 2 groups: 9 patients who survived for >3 years from SBRT and 8 patients who did not. The cutoff of 3 years was selected to obtain equal groups and to approximate the mean survival time of 3.3 years for the overall cohort. In unadjusted analysis, a linear regression model identified 20 differentially expressed microRNAs between the 2 groups; however, no differences in expression levels remained significant after Benjamini-Hochberg adjustment for the false-discovery rate. Elastic net regression, which was applied to normalized quantitative polymerase chain reaction \( C_t \) numbers, yielded a microRNA classifier that was prognostic for survival based on the expression levels of 3 microRNAs identified in the unadjusted analysis: 1 that was nonsignificantly overexpressed in patients who had oligometastases with >3 year survival (miR-23b, \( \log_2[\text{fold change}] = 1.1 \)) and 2 that were nonsignificantly overexpressed in those with <3 year survival (miR-449a, \( \log_2[\text{fold change}] = 5.2 \); miR-449b, \( \log_2[\text{fold change}] = 6.2 \).
A classifier score was derived using the coefficients obtained in elastic net regression: \((0.02 \times F_{\text{miR-23b}}) - (0.0693 \times F_{\text{miR-449a}}) - (0.0031 \times F_{\text{miR-449b}})\), where \(F_{\text{miR-x}}\) is the normalized, log2-transformed, quantitative polymerase chain reaction \(C_t\) number of miR-x. Patients with scores \(\geq 0.566\) survived significantly longer (median not yet reached vs 1 year; \(P = .002\)) than those with lower scores (Fig. 3).

DISCUSSION

We identified a subset of long-term survivors who had a median follow-up approaching 7 years in this analysis of a prospective radiation dose-escalation trial for patients with oligometastases. We observed that clinical factors, such as breast cancer, the time to metastatic diagnosis, and the rate of metastatic progression, were associated with survival. Furthermore, we identified a primary tumor-derived, 3-microRNA classifier that was prognostic for survival in these patients.

Radiotherapy dose escalation improved local control. The 5-year TMC of 69% in patients who received a minimum dose of 36 Gy in 3 fractions fell within the 65% to 95% range of local control rates published in similar SBRT experiences, most of which had shorter follow-up.6-13 Other institutions have observed that escalation to biologically effective doses >100 Gy was needed to achieve approximately \(\geq 90\%\) local control.8,13,24 Like other reports, dose escalation in our cohort failed to improve OS, likely because of high rates of failure outside of treated lesions and eventual polymetastatic progression.

Although we15 and others6,10-13,25 have reported promising clinical outcomes after ablative radiotherapy in some patients with oligometastases, similar to the outcomes reported after metastasectomy,2-5 only approximately 25% achieved long-term disease control and survival, similar to the 32% 5-year OS in the current cohort. Clinical criteria, often including histology, the number of metastases, the interval from diagnosis to first metastasis, and disease control immediately before metastasis-directed therapy, are currently used to select patients for these therapies.26 We observed that many of these criteria predicted for survival in our patients. Indeed, the strongest favorable clinical prognostic factor was breast cancer histology. Among patients in our cohort who had breast cancer, 50% remained alive and controlled at protocol-treated sites at 5 years, similar to the 6-year OS of 47% after SBRT reported by investigators at the University of Rochester.6,7

Even using optimal clinical selection criteria, most patients with oligometastases will progress shortly after receiving ablative metastasis-directed therapies.27 Recent research has identified biomarker predictors of oligometastatic tumor biology that may better select patients who are likely to benefit from aggressive local therapy. A previous analysis of primary and metastatic tumors implicated the miR-200 family of microRNAs in regulating polymetastatic versus oligometastatic progression after the completion of ablative radiotherapy.18 In a separate analysis of resected pulmonary metastases, a different microRNA profile was found to predict the rate of progression after surgery.28 More recently, we analyzed metastatic tumor samples and observed that miR-127-5p, miR-544a, and miR-655-3p, which are encoded in a cluster on 14q32, suppress cellular adhesion and invasion, inhibiting metastasis development in mouse models, potentially by targeting transforming growth factor, \(\beta\) receptor II (TGF\(\beta\)R2) and Rho-associated protein kinase 2 (ROCK2).29

In the current study, we derived a classifier that was prognostic for survival within our cohort using the expression levels of 3 microRNAs. None of the 3 was encoded on the 14q32 cluster, and none was identified in our previous report describing microRNA expression in metastatic lesions.28 The absence of overlap may result from differences in primary and metastatic tumor samples and from our selection of microRNAs that were prognostic for survival in this analysis rather than for metastatic progression, as in prior reports.

It has been demonstrated that the 3 microRNAs in our classifier regulate tumor behavior. miR-23b is a pleiotropic modulator that directly targets oncogenes and signal transducers, such as phosphatase and tensin homolog (PTEN), protein kinase B (Akt), proto-oncogene tyrosine-protein kinase (SRC), mitogen-activated protein kinase kinase kinase 1, E3 ubiquitin protein ligase (MAP3K1), TGF\(\beta\)R2, and related RAS viral oncogene homolog 2 (RRAS2), leading to inhibition of tumor proliferation, epithelial-to-mesenchymal transition, migration, invasion, and angiogenesis in vitro as well as suppression of metastasis in animal models.30-33 Clinically, miR-23b expression has been associated with improved PFS or OS in patients with ovarian, prostate, and renal cancer but with worse outcomes in patients with breast cancer.31-35 miR-449a and miR-449b, which have overlapping targets, directly interact with cell-cycle regulators and oncogenes like cyclin-dependent kinase 6 (CDK6), cell division cycle 25A (CDC25A), histone deacetylase 1 (HDAC1), hepatocyte growth factor receptor (MET), and Finkel-Biskis-Jinkins murine osteogenic sarcoma viral oncogene homolog (FOS).35-38 miR-449b
expression increases the risk of recurrence in patients with prostate cancer. 39 Paradoxically, tumor-suppressive effects of miR-449a and miR-449b have been reported in vitro. 35-38 The conflicting effects of these microRNAs in different settings reflect the complexity of their interaction with the multiple cellular pathways they regulate.

Our study has several limitations. The radiation doses initially prescribed were low compared with those commonly used in SBRT today. Our analyses were limited in statistical power, and few patients had primary tumor samples available for microRNA analysis. Patient numbers were insufficient for validation of the microRNA classifier in an independent data set. Thus, our hypothesis-generating microRNA results require confirmation in larger cohorts of patients with oligometastases once such data sets become available. Nevertheless, the study also has several strengths, such as mature follow-up, inclusion of patients with diverse primary histologies, and a molecular approach to the classification of the oligometastatic state.

The extent to which metastasis-directed therapy improves disease control or survival remains unknown. 27 Although it is interesting to speculate that control of treated metastases is needed for long-term survival, because only 2 of 13 long-term survivors had progression of a treated metastasis at last follow-up, case-control series of oligometastatic patients have not supported this finding. 40 This controversy underscores the need for randomized clinical trials, such as the recently opened phase 2/3 randomized trial for patients with oligometastatic breast cancer (NRG-BR002), as well as the ongoing Belgian STOMP trial (Surveillance or Metastasis-Directed Therapy for Oligometastatic Cancer Recurrence) for patients with oligometastatic prostate cancer and the SABR-COMET trial (Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastatic Tumors), which is enrolling patients who have oligometastases from any solid tumor primary. The UK-Australian CORE (Conventional Care or Radioablation in the Treatment of Extranodal Metastases) randomized trial is also expected to open soon.

In conclusion, our long-term data demonstrate that patients with oligometastases can receive ablative radiotherapy to all malignant sites with limited acute and late toxicity, leading to reasonable rates of TMC with sufficient dose escalation. A subset of these patients, especially those with breast cancer, may achieve long-term survival. MicroRNA classifiers may help predict tumor biology and clinical outcome. Research to validate microRNA expression profiling in the selection of optimal patients for oligometastasis-directed therapy is ongoing.

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REFERENCES


