Predicting long-term survival following involved site radiotherapy for oligometastases

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Abstract. The majority of cancer-associated mortalities are due to distant metastases, and systemic therapy alone is generally not curative. Patients with oligometastases are amenable to involved site radiotherapy with the possibility of long-term disease-free survival; however, prognostic factors remain poorly defined. The present retrospective, single institution study consisted of consecutive adult patients with oligometastases from solid tumor malignancy referred to a single high volume radiation oncologist between January 2014 and December 2021. Oligometastases were defined as ≤5 extracranial or intracranial metastatic lesions where all sites of active disease are treatable, including patients requiring treatment of the primary tumor and/or regional lymph nodes. The study population consisted of 130 patients with 207 treated distant metastases. Radical radiotherapy was administered to all areas of known residual disease and included stereotactic radiotherapy (median dose, 27 Gy in 3 fractions) or intensity modulated radiotherapy (median dose, 50 Gy in 15 fractions). At a median follow-up of 28.8 months, the median overall survival was 37.9 months with a 4-year overall survival of 41.1%. The median progression-free survival was 12.3 months and the 4-year progression-free survival was 22.6%. On multivariate an1alysis, the strongest predictors of overall survival were age, ECOG performance status, primary prostate, breast or kidney tumor and pre-radiation serum albumin (P≤0.01 for all). Overall, the present study demonstrated that long-term overall survival was possible after radical treatment for oligometastases and identified potential prognostic factors.

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Introduction

Distant metastases account for >90% of cancer deaths (1,2). Despite major advances in drug development for solid tumors, life-extending systemic therapy is generally not curative when used as a single modality (3). The oligometastasis hypothesis implies that patients with limited metastatic burden can benefit from comprehensive local treatment with the possibility of long-term disease control, particularly when combined with effective systemic therapy to prevent new metastases (4). Pioneering prospective studies conducted in the 2000's reproducibly confirmed long-term disease-free survival in 20 to 30% of patients with extracranial oligometastases long-term follow-up (5). These promising data led to randomized trials confirming improved progression-free survival and overall survival when supplementing metastasis-directed therapy to systemic therapy alone for patients with extracranial oligometastases from non-small cell lung cancer and mixed primary tumors (6,7).

Based on these data, patients with oligometastases receiving radiation therapy to all areas of known disease represent an important subset of contemporary patients referred to radiation oncology for distant metastases (8). After screening 29 clinical, pathologic, radiologic and laboratory variables, our group identified and validated 4 prognostic factors independently predicting survival in unselected patients with distant metastases referred to radiation oncology (9,10). Taken together, the components of the NEAT predictive model predicting higher survival are higher performance status, normal serum albumin, less widespread disease and breast, prostate or kidney primary tumor. A surprising finding was that brain metastases were not independently associated with poorer outcome (9).

In a recent analysis, patients with distant metastases selected for higher dose radiation defined as an equivalent dose in 2 Gy fractions (EQD2) of ≥40 Gy had a median survival of 16.0 months compared to 3.8 months for patients treated with an EQD2 of <40 Gy (8). We hypothesized that performance status, serum albumin and primary tumor type would remain robust prognostic factors in a cohort of patients with oligometastases, including limited brain metastases, treated with higher dose radiation.

The ESTRO/EORTC consensus oligometastasis classification proposed 9 distinct oligometastasis categories (2). There are emerging data suggesting that patients with induced oligometastases have worse survival that patients with de novo oligometastases or repeat oligometastases (11). The purpose of this work is to report the long-term outcomes of patients with oligometastases treated with curative intent radiotherapy in the context of the recently developed ESTRO/EORTC classification schema.

Materials and methods

Patient population. This retrospective single institution registry study was approved by the IRB #16-016 with waiver of informed consent. The study population consists of consecutive adult patients 18 years of age or older with oligometastases from solid tumor malignancy referred to a single high volume radiation oncologist (JK) between 1/1/14 to 12/31/21. Oligometastases were defined as 5 or fewer extracranial or intracranial metastatic lesions where all sites of active disease are amenable to treatment. For synchronous metastases, the primary tumor ± regional lymph nodes were also treated with radiotherapy. For metachronous metastases, the primary tumor was controlled with prior local therapy. Systemic therapy was integrated with radiotherapy at the discretion of the treating medical oncologist. Whole body imaging consisted of PET/CT or CT chest, abdomen and pelvis with bone scan ± brain or spine imaging.

Treatment and follow-up. Immobilization, simulation, radiation treatment volumes and schedules were personalized based on location, volume and organs at risk. Depending on location, volume and organs at risk, intensity modulated radiation therapy, stereotactic body radiotherapy and stereotactic radiosurgery were prescribed. Image-guided radiation therapy was delivered on the Varian TrueBeam or Varian Edge. Systemic therapy prior to, during or after radiation was administered at the discretion of the treating medical oncology and/or urologist.

Patients were followed by radiation oncology and medical oncology using an integrated electronic medical record system (EPIC) supplemented by tumor imaging and blood work. Generally, follow-up was robust with a daily inpatient oncology huddle attended by radiation oncology and medical oncology supplementing scheduled outpatient follow-up. The minority of patients lost to follow-up were supplemented by requests for office records, phone calls and review of obituary records.

Outcomes. The primary endpoints were overall survival and progression-free survival measured from date of consultation to time of event. Our group has previously demonstrated the prognostic significance of ECOG performance status, primary tumor and pre-treatment serum albumin on survival in patients with distant metastases. Additionally, we investigated the prognostic significance of ESTRO/EORTC oligometastatic disease classification, age, sex, lesion site, number of metastases treated, whether the primary tumor was also treated and systemic therapy previously reported by other authors.

Statistical analysis. Overall survival and progression-free survival were estimated using the Kaplan-Meier method. Patients lost to follow-up were censored at last known follow-up. Candidate predictors of survival were assessed using univariate Cox regression. Variables with a P-value of <0.10 were entered into multivariate Cox regression analysis. A P-value of <0.05 was considered statistically significant. All analyses were performed using Stata 13.1.

Results

Patient and treatment characteristics. The study population consists of 130 patients with 207 treated distant metastases referred to radiation oncology between 1/2014 and 12/2021. Key patient characteristics include median age 71 (range 28 to 96), 54% male, 72% ECOG 0-1 performance status, median pre-radiation albumin 3.7 g/dl, 35% lung primary, 12% prostate primary, median of 1 distant metastasis treated, 31% bone metastases, 30% brain metastases (Table I).

The most frequent ESTRO oligometastatic groups were synchronous oligometastases (40%) and metachronous oligorecurrence (29%) (Table SI). The incidence of de novo oligometastases was 77% with 11% repeat oligometastasis and 12% induced oligometastases.

A total of 69 patients received stereotactic radiation with a median dose of 27 Gy (interquartile range 27 to 33 Gy) in a median of 3 fractions (interquartile range 3 to 4). A total of 84 patients were treated with image-guided radiation therapy to a median dose of 50 Gy (interquartile range 45 to 59.4 Gy) in a median of 15 fractions (interquartile range 10 to 28 fractions). A small subset of patients underwent surgery (most commonly craniotomy). Two patients underwent interventional radiology ablation and 1 patient underwent brachytherapy (20 Gy in 4 fractions). In addition to radiation to distant metastases, 47% received synchronous treatment to the primary tumor ± regional lymph nodes.

Prior to radiation, 68% were not actively receiving systemic therapy while 12% were receiving chemotherapy alone, 7% hormonal therapy ± adjuncts such as androgen receptor blockade and/or CDK 4/6 inhibitors, 5% immunotherapy or targeted therapy alone and 8% chemotherapy in combination with immunotherapy or targeted therapy. During or following radiation, 74% received systemic therapy with diverse treatment regimens (Table SII).

Survival outcomes. At a median follow-up among surviving patients of 28.8 months (IQR 16.0 to 56.3 months), a total of 66 patients (49%) died and 92 patients (71%) experienced disease progression. The median overall survival is 37.9 months with a 4-year overall survival of 41.1% (95% CI 30.7-51.3) (Fig. 1A). The median progression-free survival was 12.3 months with a 4-year progression-free survival of 22.6% (95% CI, 14.9-31.3) (Fig. 1B).

Predictors of survival. On univariate analysis, age, ECOG performance status, primary prostate, breast or kidney tumor and albumin predicted overall survival (Table SIII). Other variables including sex, category of ESTRO/EORTC oligometastatic disease, metastasis location, number of distant metastases treated, active primary tumor requiring treatment

Table I. Characteristics of 130 patients with oligometastases.

Variable	% (n)
Age (years)	
<60	19 (25)
60-79	55 (72)
≥80	26 (34)
Sex	
Male	54 (70)
Female	46 (60)
ECOG performance status	
0	23 (30)
1	48 (63)
2	22 (28)
3 or 4	7 (9)
Category of oligometastatic disease	
De novo oligometastases (synchronous oligometastatic, metachronous oligorecurrence or metachronous oligoprogression)	77 (100)
Repeat oligometastasis (repeat oligorecurrence, repeat oligopersistence or repeat oligoprogression)	11 (14)
Induced oligometastasis (induced oligorecurrence, induced oligopersistence or induced oligoprogression	12 (16)
Primary tumor[a]	
Lung	35 (45)
Prostate	12 (15)
Breast	9 (12)
Colorectal	8 (10)
Endometrial	8 (10)
Other	29 (38)
Metastasis location	207 tumors
Bone	31 (40)
Brain	30 (39)
Lung	22 (28)
Distant Lymph Nodes	19 (25)
Liver	10 (13)
Adrenal gland	3 (4)
Albumin (g/dl)	
≥3.4	66 (86)
2.4-3.3	24 (31)
<2.4	2 (2)
Unknown	8 (11)
Number of metastases treated	
0	7 (9)
1	56 (73)
2-5	37 (46)
Active primary tumor requiring treatment	
No	53 (69)
Yes	47 (61)
Post-RT systemic therapy	
No	29 (38)
Yes	71 (92)

[a]Total percentage >100% due to rounding.

and post-radiation systemic therapy were not predictive of overall survival (Tables SI and SIII).

On multivariate analysis, age [HR 1.05 (1.02-1.08); CI: 95%; P<0.001], ECOG performance status [HR 1.69 (1.15-2.47); CI: 95%; P=0.007], primary prostate, breast or kidney tumor [HR 2.79 (1.29-6.03); CI: 95%; P=0.009] and pre-radiation serum albumin [HR 0.55 (0.35-0.87); CI: 95%; P=0.01] were independently predictive of overall survival (Table II). The previously validated NEAT model included ECOG performance status (0-1 vs. 2 vs. 3-4), primary tumor (favorable vs. unfavorable) and albumin (≥3.4 vs. 2.4 to 3.3 vs. <2.4).

When applying the NEAT model to this cohort of patients with oligometastases receiving comprehensive radiation, the median survivals by risk group for very favorable, favorable and standard risk groups were 66.0 months, 18.5 months and 12.6 months respectively (P<0.001) (Fig. 1C).

On univariate analysis, albumin, primary tumor site, induced oligometastases and >1 metastasis treated predicted for progression-free survival (Table SIII). The strongest predictors of progression free survival on multivariate analysis are albumin [HR 0.59 (0.39-0.88); CI: 95%; P=0.009] and primary prostate, breast or kidney tumor [HR 1.90 (1.06-3.38); CI: 95%; P=0.03] (Table IIB).

Discussion

This dataset is unique because it represents a large single physician experience with comprehensive radiation to all areas of known disease for oligometastases with close long-term follow-up. In the context of a busy community hospital with inpatient radiation oncology, the oligometastasis patient population includes higher proportion of patients with lung primary, brain metastases, ECOG 2 to 3 performance status and advanced age. Additionally, radiation administered included not only stereotactic radiation but also intensity modulated radiation with an EQD2 ≥40 Gy. Despite including higher risk patients, the 4-year overall survival was 41% and the 4-year progression-free survival was 23% comparable to published series with more restrictive eligibility criteria (7,12-18) (Table III). In previously published series, the 4-year overall survival was 25 to 58% (Table III). In the current study, the median survival was 38 months These results are reflective of a pragmatic community practice thus broadening access to oligometastasis treatment to include patients with brain metastases, those ineligible for stereotactic radiation and patients with induced oligometastases with disease limited to the primary site and regional lymph nodes. While patients with brain metastases were previously considered a poor prognosis cohort, modern stereotactic techniques can achieve long-term disease control (19). In this series, site of metastases including brain metastases did not predict survival. Finally, the patient population treated in a community hospital with a busy emergency room skewed older with a median age of 71 compared to prior studies with a median or mean age of 63 to 69 (Table III). On multivariable analysis, older age was predictive of shorter overall survival.

In this present study, the treating radiation oncologist treated 16 new oligometastases patients per year while treating an average of 71 new patients with distant metastases per year (8). These data suggest that ~20% of patients with distant

Table II. Multivariate analysis for overall survival and progression-free survival.

A, Overall survival

Variable	HR (95% CI)	P-value
Age (years; continuous)	1.05 (1.02-1.08)	0.001
ECOG performance status (continuous)	1.69 (1.15-2.47)	0.007
Primary tumor site (breast, prostate or kidney vs. other)	2.79 (1.29-6.03)	0.009
Albumin (g/dl; continuous)	0.55 (0.35-0.87)	0.011
Induced oligometastases (no vs. yes)	1.39 (0.68-2.88)	0.369

B, Progression-free survival

Variable	HR (95% CI)	P-value
Albumin (g/dl; continuous)	0.59 (0.39-0.88)	0.009
Primary tumor site (breast, prostate or kidney vs. other)	1.90 (1.06-3.38)	0.031
ECOG performance status (continuous)	1.22 (0.90-1.66)	0.203
No. of metastases treated (0 to 1 vs. ≥2)	1.29 (0.81-2.07)	0.272
Age (years; continuous)	1.01 (0.99-1.03)	0.312
Induced oligometastases (no vs. yes)	1.28 (0.67-2.44)	0.458

HR, hazard ratios; CI, confidence intervals; ECOG, Eastern Cooperative Oncology Group.

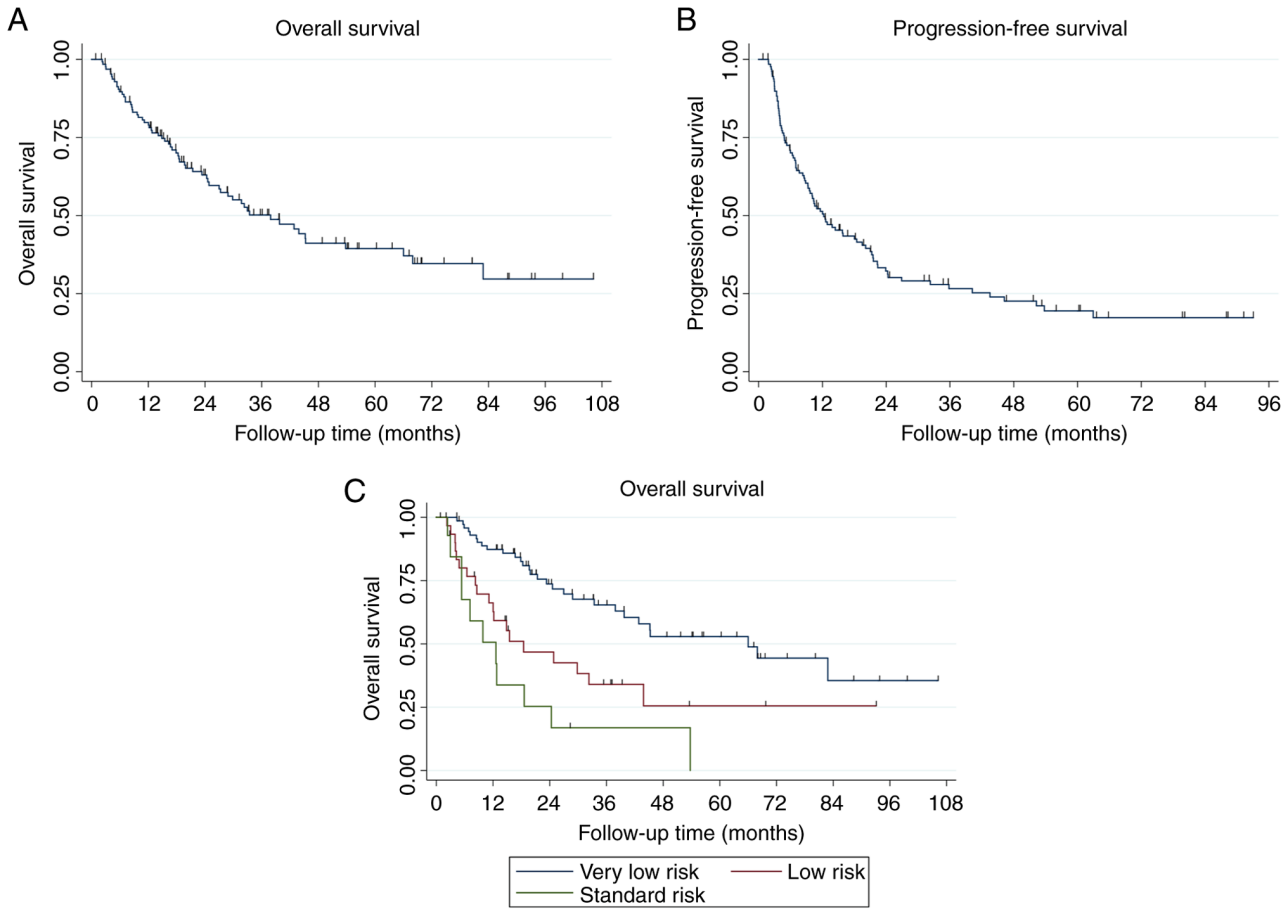

Figure 1. Overall and progression-free survival for all 130 patients with oligometastases treated with comprehensive involved site radiotherapy. (A) Median overall survival was 37.9 months and 4-year overall survival was 41%. (B) Median progression-free survival was 12.3 months with a 4-year progression-free survival was 23%. (C) Overall survival stratified by the previously validated NEAT prognostic score with median survivals of 66.0, 18.5 and 12.6 months for very low, low and standard risk patients, respectively.

Table III. Selected studies of oligometastases with long-term follow-up.

Study	No. of patients	Age (years)	Median OS (months)	Long-term OS	Long-term PFS	Performance status	Primary tumors	Brain metastasis (%)	Other patient selection notes	(Refs.)
Multi-institutional-Duke University	361	63 (median)	47	3-year OS 56%	3 year PFS 24%	Not reported	19% colorectal 17% lung 16% breast	0	- ~40% lung metastases	(15)
Multi-institutional-University of Toronto	1,033	68 (mean)	44	5-year OS 35%	5-year PFS 15%	Not reported	25% lung 23% colorectal 13% prostate	0	-Induced oligometastases excluded -45% lung metastases	(16)
National Health Service registry	1,422	69 (median)	Not reached	2-year OS 79%	2-year MFS 52%	95% ECOG 0-1	29% prostate 28% colorectal 10% renal	0	-1 to 3 metachronous extracranial metastases or synchronous colorectal liver metastases -31% lymph nodes -29% lung metastases	(13)
NRG BR-001	39	63 (mean)	Not reached	2 year OS 57%	Not reported	92% ECOG 0-1	33% breast 33% lung 33% prostate	0	-2 to 4 distant metastases	(18)
SABR-5	381	68 (mean)	Not reached	4-year OS 58%	4-year PFS 29%	96% ECOG 0-1	32% prostate	1	-40% bone metastases -35% lung metastases	(29)
SABR-COMET	66	67 to 69 (median)	50	5-year OS 42%	5-year PFS 17%	100% ECOG 0-1	21% prostate 20% breast 18% lung	2 (of metastatic lesions)	-43% lung metastases -35% bone metastases	(6)
University of Pittsburgh	147	63 (median)	42	5-year OS 43%	5-year MFS 17%	100% Zubrod 0-1	22% lung 21% colorectal 11% head and neck	1	-Excluded synchronous oligometastases -52% lung metastases	(17)

Table III. Continued.

Study	No. of patients	Age (years)	Median OS (months)	Long-term OS	Long-term PFS	Performance status	Primary tumors	Brain metastasis (%)	Other patient selection notes	(Refs.)
Vrije Universiteit Brussels	309	63 (median)	24	4 year OS 25%	2-year PFS 10%	KPS 80 to 100	33% lung 33% colorectal cancer 11% breast	35	-29% lymph node metastases	(14)
Current study	130	71 (median)	38	4-year OS 38%	4-year PFS 23%	72% ECOG 0-1	35% lung 12% prostate 9% breast	30	-31% bone metastases	

PFS, progression-free survival; OS, overall survival; ECOG, Eastern Cooperative Oncology Group.

metastases referred to radiation oncology have oligometastases amenable to metastasis directed therapy. With respect to patient selection, there were 4-year survivors across all subgroups examined with the exception of small cohorts of ECOG 3-4 (n=9), albumin <2.4 (n=2), repeat oligoprogression (n=5) and induced oligorecurrence (n=2).

Predicting outcome for patients with oligometastases is particularly important because a basket design is pragmatic for accrual purposes but is inherently heterogeneous (20). Our group previously developed and validated the NEAT model for patients with distant metastases referred to radiation therapy that included oligometastases (9,10). The prognostic factors contributing to the NEAT model also independently predict overall survival in this cohort of patients with oligometastases. Patients with oligometastases had numerically higher survival by NEAT grouping compared to the entire cohort of patients with distant metastases -66.0 vs. 29.5 months for very low risk, 18.5 vs. 11.8 months for favorable and 12.6 months vs. 4.9 months for intermediate risk. These findings provide further evidence that treating all areas of known involvement contributes to improved progression-free survival and overall survival.

Confirming prior research, patients with induced oligometastases have a numerically worse overall and progression-free survival in the present study (11,12). The notion that synchronous oligometastases may have worse outcomes than metachronous oligometastases informed design of the ESTRO/EORTC classification system (2). Due to small numbers, any observed differences in survival in this study were only marginally significant on univariate analysis and was not statistically significant on multivariate analysis. The authors eagerly await prospective data on the oligometastatic disease classification through the ongoing OligoCare study for further clarification regarding the prognostic significance of the ESTRO/EORTC classification.

The present study highlights the importance of albumin in predicting survival for patients with distant metastases, including oligometastases. In a systematic review, pretreatment serum albumin provides useful prognostic information across various types of cancer (21). While there is great interest in emerging biomarkers such as circulating tumor DNA (ctDNA), comprehensive genomic testing and PD-L1, there is currently only minimal interest in utilizing serum albumin as a simple, widely available and low cost biomarker for future radiation oncology trials investigating metastatic disease (22).

The finding that age impacted survival was not seen in prior analyses of patients with unselected distant metastases or oligometastases (9,10). The present study included 26% of patients age ≥80 and advanced age is a risk factor for all-cause mortality, particularly during the SARS-CoV-2 pandemic (23). Although 64% of patients age ≥80 in the present study received systemic therapy, frailty upon progression certainly limited the availability and effectiveness of salvage systemic options with earlier initiation of transition to hospice.

This study should be interpreted in the context of both strengths and limitations. First, this is a single physician study performed by an investigator with extensive experience in safely treating oligometastases for over a decade and interest in prognostication to inform treatment decisions. Therefore, these findings may not be generalizable to other

settings. Second, patient numbers were insufficient to make definitive conclusions about small subsets including individual ESTRO/EOTRC oligometastatic disease classifications. Although single physician series are currently out of vogue because of inherently lower sample sizes, data quality may be higher because each patient is well known to the treating physician who also performs longitudinal follow-up. The community hospital setting has unique strengths because distance travelled is shorter and patients and their families tend to rely on their local healthcare infrastructure for acute hospitalizations towards the end of life rather than traveling to more distant quaternary facilities (24). The recent implementation of multidisciplinary daily oncology rounds further enhances the quality of longitudinal follow-up. Finally, it is important to promote the inclusion of the perspectives of a community oncology practice serving a racially and economically diverse community with more limited resources in contrast to major academic centers (25).

In terms of future directions for treatment of oligometastases, further drug development would reduce the incidence of early progression (1,3). Integrating ctDNA could allow for earlier and more effective use of salvage therapies, including repeat stereotactic body radiotherapy (26). Utilizing genomic information could achieve more precise prognostication to reduce futile therapy. Optimizing cancer survivorship for long-term survivors of distant metastases is another important avenue of research (27,28). Finally, validating accurate predictors of early widespread progression after metastasis directed therapy could lead to the design of more effective treatment strategies and avoiding futile therapy (29).

In conclusion, long-term overall survival is possible after radical treatment for oligometastases in the real world setting. The ESTRO classification provides an enriched nomenclature for oligometastases but is not independently predictive of overall survival.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JK and AS contributed to the conception and design of the study. JK, PE, JM, CA and AS contributed to the acquisition, analysis and interpretation of the data, and contributed to manuscript drafting and critical revisions on the intellectual content. All authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work. JK and PE confirm the authenticity of all the raw data.

Ethics approval and consent to participate

This retrospective single institution registry study was approved by the Good Samaritan University Hospital (approval no. IRB #16-016) with a waiver for informed consent.

Patient consent for publication

Not applicable.

Competing interests

JK served on Advisory Boards for Astra Zeneca and previously led an educational webinar for Varian. The other authors declare that they have no competing interests.

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