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Title	Tumour-specific growth rate as a potential predictor of outcomes in oligoprogressive disease treated with stereotactic body radiotherapy
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Publication date	2025-06-18
Original Citation	Navarro-Domenech, I., Helou, J., Thomas, S. K., Dawson, L. A., Hosni, A., Raman, S., Chung, P., Wong, R., Glicksman, R., Lindsay, P., Javor, J., Weiss, J., Hope, A. J. and Barry, A. S. (2025) 'Tumour-specific growth rate as a potential predictor of outcomes in oligoprogressive disease treated with stereotactic body radiotherapy', Clinical Oncology, 44, 103895 (10pp). https://doi.org/10.1016/j.clon.2025.103895
Type of publication	Article (peer-reviewed);journal-article
Link to publisher's version	10.1016/j.clon.2025.103895
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Download date	2026-11-16 07:05:40
Item downloaded from	https://hdl.handle.net/10468/17706

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Introduction

The use of stereotactic body radiotherapy (SBRT) in the treatment of oligometastatic disease (OMD) has shown benefit in long-term overall survival (OS) compared to maintenance or standard of care/systemic treatment alone. [1,2],[3] Guckenberger et al. [4] initiated The European Society for Radiotherapy and Oncology/European Organisation for Research and Treatment of Cancer (ESTRO/EORTC) consensus for the characterization of the OMD group, which included the terms and sub-classifications of oligoprogressive disease (OPD), [5] recognising the heterogeneity amongst patients with metastatic disease and the increasing variability in therapeutic options and clinical goals.,[4], [5]

Patients with OPD are generally defined as having multi-metastatic sites of disease with a few (often ≤5 metastatic lesions) areas of progression on radiological imaging, with the rest of the disease remaining stable on systemic therapy. [4] This entity is clinically different to the other OMD categories, [4] and published data reports lower progression free survival (PFS) and OS [6–10] compared to OMD. The treatment goal thus far has focused on maintaining patients on the current line of systemic therapy, rather than a more "curative" intent as in OMD. [11–13] However, the benefit of SBRT appears to be influenced by the different tumor types. [14],[15]

The tumour-specific growth rate (SGR) is a quantifiable characteristic of a tumour that reflects its growth kinetics, depending on factors such as cell type, growth fraction, and clinical stage. It is mathematically related to tumour doubling time (TDT), which measures the time required for a tumour to double in volume. These measures are inversely correlated, with SGR = ln(2) / DT, meaning that faster-growing tumours have a shorter TDT and a higher SGR, and vice versa. While both metrics provide insights into tumour growth dynamics, SGR expresses the relative percentage increase in tumour volume per unit time, whereas TDT provides an absolute

time-based measure of tumour expansion and being used, for example, as an indicator of the pace of the disease in prostate cancer, taking into account the speed of PSA increase over time. The TDT may express more uncertainty and does not consistently reflect differences in tumor growth rates across all ranges. SGR has been studied in early-stage lung cancer treated with SBRT, where a high SGR was associated with poorer progression-free survival (PFS). Given the limited understanding of which patients benefit most from local ablative therapies, incorporating clinical variables such as SGR—and potentially TDT—may offer additional guidance for clinicians [16]. This study aims to assess correlation between pre- and post-treatment SGR and, the histology and cancer control outcomes, for oligoprogression (OP) metastases treated with SBRT.

Material and Methods

Patients eligible for metastases directed SBRT, with 5 or less OP metastases of different histologies were enrolled onto a prospective single arm phase II study (XXXXXXX) between October 2019 and March 2021. An unplanned post-hoc secondary analysis was performed using this dataset.[17] For statistical purpose, patients were grouped based on the area/characteristics of primary tumour in gastrointestinal (GI), breast or genitourinary (GU) cancer groups.

As part of the trial follow-up, at least a CT-CAP was performed at 3-4 monthly intervals as deemed appropriate by treating physician, but MRI may be used also in bone and liver metastases. Baseline and follow-up SBRT CTs, within 3 months previous to and after the planning CT, were imported into the treatment planning system (Raystation V8B). Treated OP metastases were reviewed by a board certified radiologist (SKT) and contoured by a board certified radiation oncologists (IND) as gross tumour volume oligoprogressive (GTV_OP) on pre-SBRT diagnostic

images (GTV_OP1), at the time of planning SBRT (GTV_OP2) and post-SBRT (GTV_OP3) to determine the volume of each metastasis at each timepoint. In the setting of multiple OP metastases an Index lesion was identified at baseline as per study protocol, this Index lesion was contoured on each scan. Only patients with available scan images were included. The macroscopic tumour (gross tumour volume) for each oligoprogressive lesion was defined as the volume for study. In cases where the lesion was indistinguishable from postradiotherapy/fibrosis changes, the entire volume was delineated. No margins to account for planning target volumes were applied to the contours. Tumour specific growth rate (SGR) was calculated according to the literature as (ln(GTVy/GTVx)/t) %/d.[18] The time interval is quantified from the diagnostic CT scan until the date of SBRT planning CT (time 1, t=1), and from planning SBRT CT date until the follow-up CT scan after SBRT treatment (time 2, t=2), where "t" is measured in days. [18] Time zero (t0) was defined as the date of planning SBRT CT. SGR_ oligoprogressive (SGR_OP)1 was defined as pre-SBRT growth (from SBRT CT scan to baseline imaging); and SGR_OP2 as post-SBRT (from follow-up CT to planning CT). Based on the calculation of the median SGR_OP1/2, it was dichotomized in high SGR_OP1/2 defined as greater than the median SGR_OP1/2 value for each population, and low SGR_OP1/2 defined as any value below the median.[18]

The primary endpoint was to determine if there is a correlation between SGR_OP1/2 and overall survival (OS), comparing patients of different cancer group. The secondary objective was to assess the association of SGR_OP1/2 with progression, defined as local progression (LP) or disease progression (DP), exploring intra- patient and inter-lesion when patients have more than one OP lesion variation using a box plot diagram. For patients with multiple lesions, the highest SGR value was used for progression and OS analyses.

Statistical analysis

Demographics were summarized on a per lesion and per patient basis. Continuous variables were summarized using mean ± standard deviation (SD) and median/ inter-quartile range (IQR), and categorical variables were summarized using counts and percentages. The association between the cancer group and SGR_OP1/2 with time to progression was analyzed using linear mixed models, adjusting for multiple lesions from the same patient. A univariate analysis of predictors of survival, including patient characteristics and SGR_OP1/2, was conducted using the Wilcoxon rank sum test and Kruskal-Wallis test for continuous variables, and the Chi-Square/Fisher's exact test for categorical variables.

Overall survival (OS) was defined as the time since planning SBRT CT date until the time of death, local progression (LP) as the time from SBRT-treated lesion to radiographic progression as per RECIST v1.1 criteria, and disease progression (DP) as the time of any progression at any site. For these three events of interest, the time points used was calculated in months from the date of planning SBRT. The OS rates were estimated using the Kaplan-Meier method and compared between cancer group using Cox proportional-hazards models. Progression rates were estimated using the cumulative incidence function with competing risk of death, and compared using Fine-Gray subdistribution hazard models.

Results

A total of 35 patients with 55 treated metastases, contoured on pre- and post-SBRT imaging CT, were included in this analysis. Median patient age was 69 (IQR 58 - 73.5) years. Ten (29%) patients belonged to breast cancer group, 11 (31%) to the GU cancer group and 14 (40%) to the GI cancer group. All analyzed patients were classified with oligoprogressive disease, a condition

of the phase II study they were included on. According to the ESTRO/EORTC consensus, all the patients were categorized as having de novo or repeated metastases, of these all were diagnosed with genuine OMD. Seventy-seven percent (n=27) were repeat oligoprogression while 17% (n=6) metachronous oligoprogression (*figure 1*). Two patients (6%) were initially diagnosed with synchronous oligo-metastatic disease but received subsequent treatment when those lesions progressed.

Twenty-two (63%) patients had one OPD metastases treated and the most common location was in the abdomen (66%). Different radiotherapy schemes, including 1 to 5 fractions, were used. The majority of patients received 5 fractions of SBRT (89%) with a median dose delivered 35 Gy (IQR 30, 40 Gy). Median baseline GTV_OP volume for patients with high SGR_OP1 and SGR_OP2 was 11.71 cc (IQR 4.81, 21.18 cc) and 10.02 cc (IQR 2.58, 19.14 cc). Patient characteristics are summarized in table 1.

SGR_OP1/2 per cancer group.

The median SGR_OP1 was 0.007%/d (IQR 0.004, 0.013; range -0.01, 0.03), and SGR_OP2 -0.009%/d (IQR -0.014, 0.002; range -0.03, 0.02). Median tumour doubling time (for time 1 and time 2) was 82.9 days (IQR 49.2 – 131.5). Forty-eight percent of patients had a high SGR_OP1 (>0.007%/d) and 50% high SGR_OP2 (> -0.009%/d). The median time between baseline diagnostic CT and planning CT (t=1) for high SGR_OP1 was 79.5 days (IQR 53.25, 105 days), and 101 days (IQR 50.25, 139 days) between planning CT to follow-up CT for high SGR_OP2. Patients in the GI group demonstrated a greater proportion of patients with high SGR_OP1, which was not statistically significant when compared to patients with GU and breast cancers [67%, 45% and 30%, respectively (p=0.26)]. Similar SGR_OP2 rates between groups were seen in the post

SBRT comparison [62%, 25% and 2%, respectively (p=0.17)]. In addition, intra-patient and inter-lesion variability in the SGR_OP1/2 proportion rate was observed (Figure 2a,b).

Clinical outcomes.

Median follow-up was 11.7 months (IQR 8.1 - 15.6 months). Cancer specific death occurred in 16 (46%) patients. At 12-months the overall survival (OS) rate for all patients was 59% (95% CI, 44 - 78). The 12-month OS by cancer group was: 14% (95% CI, 4 - 51.5) in GI versus 90% in GU (95% CI, 75 - 100) and breast (95% CI, 73 - 100) cohorts, and when evaluated based on SGR_OP1, OS was 71% (95% CI, 52 – 96) for low SGR_OP1 vs. 47% (95% CI, 27 – 81) for high SGR_OP1. On univariate analysis, OS was significantly different between cancer groups (p=0.003), however, there was no significant difference in OS between patients with a low SGR_OP1 compared to high SGR_OP1 (p=0.35) (*Figure 3 a, b*).

Overall five (14%) patients, with six SBRT-treated metastases, developed local progression (LP). Four (9%) patients belonged to the GI group, and 1 (3%) from breast cancer group. Disease progression (DP) of other non-SBRT treated metastases occurred in 29 (83%) patients. At 12-months, the LP and DP was 11% (95% CI, 3.5 - 24.5) and 77% (95% CI, 58 - 88), respectively.

At 12-months, all patients that developed LP belonged to had GI cancer group (29%, [95% CI, 8 – 54]) and had high SGR_OP1 (19%, [95% CI, 4 – 41]) (*figure 4.a, b.*). However, on the univariate analysis none other variable demonstrated a statistically significant association with local progression. In particular, we did not observe any correlation between LP with cancer group (p=0.083) nor SGR_OP1 (p=0.28) (*Table 2*).

Patients into the GI cancer group experienced a greater rate of disease progression (DP) compared to GU and breast groups (93% [95% CI, 39 – 99] vs. 73% [95% CI, 25 – 93] and 60% [95% CI, 22 – 84], respectively); and is more likely to have higher values rate of SGR_OP1 at 12-month (93% [95% CI, 41 – 99.5]). Cancer group was statistically significant on univariate analysis (p=0.031), however no significant association was seen with SGR_OP1 (p=0.055) (*figure 4 c,d*) or SGR_OP2 (p=0.89).

Discussion

This is the first study in the setting of oligoprogressive disease treated with SBRT to analyze the impact of pre- and post-treatment tumour SGR_OP1/2 as a predictive factor of OS and disease progression, especially SGR_OP1 (pre-SBRT growth). SGR_OP1 and SGR_OP2 median values (0.007%/d and -0.009%/d, respectively) were used as a cut off to stratify OP patients into risk groups. Although not statistically significant, patients with high SGR_OP1/2 had numerically lower rates of survival and a higher probability of developing tumour progression. In addition, we found that gastrointestinal tumours were associated with higher SGR_OP1/2 and therefore poorer survival outcomes.

Following the significant improvement in clinical imaging techniques, and metastasis–directed treatment (MDT); [11,19] there is a greater interest in the use of radiomics as a predictor of response after SBRT.[20–22] Tumour SGR has been studied as an initial radiomic tool to understand cancer biology in preclinical studies. [23,24] In 1990, the correlation between the

156 growth of a metastasis in a mouse and the primary tumour found that metastatic SGR differs from
157 the primary tumour, and it is greater in a metastatic implant compared to the growth of the primary
158 tumour which may explain differences in the response of metastases to oncologic treatments i.e.
159 metastases with a lower SGR compared to the primary tumour could be more resistant to
160 chemotherapy agents. [23] This theory could explain the better outcomes of SBRT in low SGR
161 tumours, since it could be more sensitive to ablative dose of radiation.

162 Despite the lack of studies in this area, SGR has been found to have prognostic value in breast
163 cancer in the preoperative period determined by ultrasound (US). [25] The authors found that SGR
164 was higher when initial tumours were smaller, and higher SGR was associated with
165 lymphovascular invasion, lymph node spread and higher histologic grade. They concluded that
166 higher SGR was associated with worse disease-free survival. Comparable results were also studied
167 in oropharyngeal cancer[26] and in cervical lymph nodes (LN-SGR) for head and neck squamous
168 cell carcinoma (HNSCC).[27] Clinical tumour growth rates are influenced by specific histologies
169 and biomarkers, which could help predict treatment failure. These finding are in agreement with
170 our results.

171 Shin et al. analyzed 86 patients with metastatic melanoma treated with pembrolizumab in the
172 oligometastatic setting. [28] The authors assessed the gross tumor volume of all metastases
173 (median 7, range 1 – 73), and since tumor growth did not follow a normal distribution, the cohort
174 was divided into quartiles. Patients with a slow growth rate had higher OS and PFS compared to
175 those in the 'fast-paced' group, with further differences more prominent in those with a greater
176 burden of disease (>5 metastases). The population analysed by Shin et al appears to consist of a
177 spectrum of metastatic disease - those with either a new tumour recurrence (e.g. metachronous
178 oligo-metastatic/oligorecurrent) or new metastases after prior treatment (e.g.

oligoprogressive/oligorecurrent), with 72% treated with systemic pembrolizumab as first line therapy to prolong survival and/or disease progression. On the contrary, the population in this study was predefined as oligoprogressive, with all patients receiving systemic treatment and all patients receiving local ablative treatment for minimally progressive disease with the intent to control disease and delay next line of systemic treatment. However, despite these differences it does appear that SGR may be a unifying prognostic indicator, how to incorporate this into clinical use requires further review.

In non-small cell lung cancer(NSCLC), pre-treatment SGR has been analyzed as a prognostic factor to response to mutation-directed therapy (e.g. in patients treated with Erlotinib, an epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI)),[29] as well as to chemoradiation treatment for locally advanced NSCLC [30]. In both studies, a high SGR was associated with poorer outcomes. Atallah et al. [18] analyzed SGR of 160 patients with stage I NSCLC treated with SBRT, reporting lower OS in the high SGR cohort (38 vs. 66 months, $p=0.03$) in addition to lower failure-free survival (FFS) (27 vs. 55 months, $p=0.005$). In this analysis male gender and SBRT volume were associated with worse OS ($p<0.001$). Although our study does not include primary lung cancer, these results are consistent with our results.

SBRT is reported as providing excellent local control rates in the setting of metastatic disease, consistent with the present study reporting a LC rate of 89% at 12-months. In patients who experienced local progression, the majority had GI cancers and exhibited a higher tumor SGR_OP1, resulting in a greater local progression rate of 25% within the first 6 months, in contrast to no progression observed in the GU/Breast and low SGR_OP1 groups, which only showed progression after 15 months. This suggests that the GI cohort showed a more aggressive pattern at the time of progression compared to the other studied population (GU/breast).[31] Nevertheless,

the intra-histological variations are also remarkable. For instance, in tumors that might initially appear to exhibit slow growth (such as prostate cancer in the GU category), we observe a distribution of cases across the entire axis in the box plot diagram, including instances of rapid progression. Overall, we detected overlapping of SGR between the different histological categories, suggesting that histology may be of agnostic value in the selection of the patients.

In 2021, the European Society for Medical Oncology (ESMO) published the impact of SGR on the response to immunotherapy in advance gastric cancer, and how one treatment could be more favorable depending on this factor. [32] They retrospectively analyzed 117 patients treated with Nivolumab and Irinotecan and divided into slow and rapid growth. Tumour growth rate (TGR) was calculates bases on RECIST criteria [33] as $TGR=100(D_0 – D_{-1})/D_{-1}(CT_0 - CT_{-1})$, where CT_0 represents the date of diagnosis progressive disease, CT_{-1} represents the date of previous CT, and Dn represents the sum of the target lesion diameters. The response rate with Nivolumab was higher in the low SGR group without new lesions compared to the high SGR group with new lesions (31% vs. 5%, respectively). In view of these results, a relationship may be established between the response to target treatments (SBRT and immunotherapy) and SGR. The analysis of the tumour SGR could be used as a predictor of response and would allow a better selection of patients to offer local/target treatment vs. subsequent systemic therapy.

This study has some limitations. This is a retrospective analysis of a prospective study with a small number of patients. Tumour contours were delineated retrospectively on diagnostic and planning CT, which differed in resolution, use of IV contrast and slice thickness, which may affect delineation.[18] Especially, contouring uncertainty in small lesions may heavily influence in SGR measurement.[34] In terms of follow-up CT scan delineation, the tumour volumes defined did not include a treatment target volume (ie. planning target volume) to account for any potential loco-

regional fibrotic change.[35] However, it may be too early to see this type of change, additionally none of the tumour volumes delineated were increased compared to baseline potentially supporting this theory.[35] Abdominal SBRT was the most common site of treatment; therefore due to the proximity of the organ at risk (OAR), treatment planning may require an adjustment of the total dose (reduced), which may have an impact on local control. However, although patients with more than one metastatic lesion were included in the analysis, the limited number of subjects prevented a thorough examination of the relationship between SGR_OP and disease burden (number vs. volume of metastases), which may be related to a worse prognosis.[36] Although all the patients were on systemic treatment, we did not analyze the type received (chemotherapy, immunotherapy or target therapy), the duration of time of treatment, or perform specific molecular analysis. Such factors may be confounders in defining the low and high rates of SGR in this cohort of patients. Lastly, the method of SGR_OP calculation was based on a previous study assessing lung tumours, there may be additional ways to further classify low and high growth rates by using quartiles or total tumour volume. Greater patient numbers are required to ensure robust analysis of different potential methods, such as tumour doubling time (TDT), that may provide further insights into patient stratification and treatment decision-making.

Suggested future directions should attempt to incorporate SGR and its correlation with systemic treatment and tumour response in a predictive model to help in deciding which patients may benefit most from local treatments such as SBRT. Furthermore, improvement in the development of measurement and imaging tools through the use of artificial intelligence should be considered. Validation is required in a much larger number of patients including specific histologies in each group and the impact of systemic treatment on the behavior of SGR.

Translational and molecular tools may also help classify this group of patients with OPD, and establish its relationship with SGR and the response to cancer treatments.

Conclusion

In this study, we observed a tendency towards diminished cancer control and increased tumour aggressiveness in cases with a high SGR_OP compared to those with a low SGR_OP, though our findings did not achieve statistical significance. SGR_OP analysis appears to demonstrate a wide range of growth rates within individual cancer group and may allow prediction of patient outcomes independent of histology. Additional validation will be required to confirm if this tool can be used to predict outcomes.

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403 *Table 1. Patient's characteristics.*

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405 *Table 2. Univariate analysis of predictors of survival (correlation with local progression).*

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407 *Figure 1. ESTRO/EORTC definition of oligometastatic disease of patients included in this*
408 *analysis.*

409

410 *Figure 2. a) Box plot for SGR_OP1 per cancer group. b) Box plot for SGR_OP2 per cancer*

411 *group.*

412 *Along the entire axis in the box plot diagram, intra-histological variations are detected within*
413 *each cancer group, as well as overlapping of SGR_OP1/2 values among the different categories.*

414

415 *Figure 3. a) Kaplan-Meier curve demonstrating overall survival (OS) per primary tumour cancer*
416 *group. b) Kaplan-Meier curve for specific growth rate pre-SBRT (SGR_OP1) - OS. High*
417 *SGR_OP1 is defined as a value more than the median (>0.007).*

418

419 *Figure 4. a) Cumulative incidence of local progression (LP: defined as SBRT treated metastases)*
420 *per primary tumour cancer group. b) Cumulative incidence of LP per SGR_OP1. c) Cumulative*
421 *incidence of distant progression (DP: defined as non-SBRT treated metastases progression) per*
422 *.cancer group. d) Cumulative incidence of DP per SGR_OP1.*