Published in final edited form as:

Oral Oncol. 2016 December ; 63: 16–22. doi:10.1016/j.oraloncology.2016.10.022.

CT-based Volumetric Tumor Growth Velocity: A Novel Imaging Prognostic Indicator in Oropharyngeal Cancer Patients Receiving Radiotherapy

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Introduction

Numerous studies have shown that three-dimensional (3D) overall tumor volume predicts local control in squamous cell carcinomas of the head and neck even more strongly than tumor (T) staging.^{1–4} Surprisingly, however, this relationship is controversial in the subset of oropharyngeal squamous cell cancers (OSCC).[†] Multiple studies have shown no significant relationship between tumor volume and local control in these patients.^{5–8} However, at least three studies have shown that tumor volume in patients with OSCC more strongly predicts local control than T staging.^{6,9,10} Hermans et al. also have shown that nodal tumor volume is significantly associated with regional control in patients with tonsillar OSCC.⁶

Even though the evidence on the predictive potential of gross tumor volume has been equivocal, a handful of studies have shown that metabolic tumor volumes obtained from¹⁸F-

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[†]Non-standard abbreviations: oropharyngeal squamous cell cancer (OSCC); tumor growth velocity (TGV); nodal growth velocity (NGV).

fluorodeoxyglucose (FDG) positron emission tomography (PET) scan predict disease progression and survival in oropharyngeal squamous cell cancers.^{11–13} Recently, Chu et al. also demonstrated that metabolic volumetric tumor growth velocity calculated from serial PET-CT scans predicts disease progression and overall survival in patients with all head and neck cancers treated with definitive radiation, although metabolic nodal tumor growth velocity did not.¹⁴

To date, the prognostic effects of *gross* volumetric tumor growth velocity (TGV) or nodal growth velocity (NGV) have not been studied in patients with oropharyngeal squamous cell carcinoma. Presumably, TGV and NGV likely reflect *in vitro* tumor aggressiveness for these patients. Johnson et al.⁴ have used static volumetric gross tumor analysis data from head and neck cancer patients fit to statistical mixture modelling to validate the theoretical expectation of linear increase of clonogen number with volume, suggesting that there is a radiobiological basis for the hypothesis that calculations of linear TGV and NGV may predict disease progression and consequentially, survival.

To this end, the purpose of this investigation is to calculate linear TGV and NGV from serial pretreatment CT scans and assess their prognostic impact for patients with oropharyngeal squamous cell carcinoma.

Methods and Materials

Patients

After Institutional Board Review approval, we retrospectively reviewed the medical records of 1,088 patients with oropharyngeal carcinoma treated with radiation at MD Anderson Cancer Center between September 1978 and April 2008. Inclusion criteria were: 1) pathological diagnosis of oropharyngeal squamous cell carcinoma, 2) curative intent radiation therapy 3) availability of more than one pretreatment CT scans with radiographically visible primary tumors and/or pathologic nodes, 4) time interval of at least 2 weeks between the CT scans with no further treatment interventions. Patients were excluded for the following reasons: non-squamous histology, improper image format or absent images in EMR, prior surgery or induction chemotherapy, or any therapy during scan interval. A total of 101 patients who were treated between November 2004 and February 2008 met these criteria.

Imaging

All included patients had two sets of pretreatment CT scans available for review and analysis of volumetric data. The first CT scan was either done at an outside hospital for diagnostic and/or staging purposes or done at MD Anderson for diagnostic reasons. The second CT scan was performed after at least 2 weeks at our institution for diagnosis, staging, or radiotherapy planning. PET-CT scans were included, and segmentation was guided by PET if available. Volumetric data was collected using VelocityAI v.3.01 commercial software (Varian Medical Systems, Atlanta, GA) to segment primary tumor and significant nodal targets on both scans. Tumor volumes were initially measured by a medical student, and subsequently reviewed by two radiation oncologist with expertise assessing tumors of the

head and neck (ASRM, CDF). Linear TGV and nodal growth velocity were calculated from the serial measurements as percentage tumor growth per days as illustrated in the following equation:

$$\left[\frac{\text{Tumor volume at time point 2} - \text{Tumor volume at time point 1}}{\text{Tumor volume at time point 1}} / \text{duration between both scans in days} \right] \times 100$$

Additionally, volumetric tumor doubling time was calculated as described by Mordecai Schwartz¹⁵:

$$t_D = \frac{t \log 2}{\log V_t / V_0}$$

Where t_D is volumetric doubling time, t is time gap between the two scans, V_t is tumor volume at time point 2, and V_0 is tumor volume at baseline.

Treatment

Multidisciplinary treatment strategy was previously described by Garden, et al.¹⁶ Surgery before radiation was generally used for diagnosis only, while neck dissection after radiation was done for patients who did not have a complete clinical response. Concurrent chemoradiation was recommended for patients with more advanced T-stage or bulky adenopathy, and induction chemotherapy recommended for patients with advanced nodal disease. In terms of radiation, 66 Gy was prescribed for patients with small volume primary disease, and 70–72 Gy for more advanced disease. Patients were planned using the Pinnacle planning system (Philips Medical Systems, Andover, MA) and IMRT was used to treat the primary tumor and upper neck nodes using Varian (Varian Medical Systems, Palo Alto, CA) linear accelerators delivering 6-MV photons.

Statistical analysis

Recursive partitioning analysis identified velocity cut points associated with outcomes. Kaplan-Meier survival calculations were used to analyze disease control and overall survival. Comparisons between higher and lower velocity groups were made using Wilcoxon test. Cox regression, univariate, and multivariate analyses were also performed. All analyses were performed using JMP Pro statistical software version 11.2.0 (SAS Institute Inc, Cary, NC). P values less than 0.05 were considered significant.

Results

Patient Characteristics

All 101 patients in this study underwent radiation. 14 patients underwent induction chemotherapy followed by chemoradiation, 10 patients underwent induction chemotherapy followed by radiation alone, 59 patients underwent chemoradiation, and 18 patients underwent definitive radiation alone. Median follow-up was 59 months (range between 7–118 months).

93 patients had radiographically visible primaries and had TGV evaluated. Eight patients had radiographically visible nodal disease but not primary disease. Six patients did not have radiographically visible nodal disease due to excisional disease, and 11 patients did not have nodal involvement. No patients had metastatic disease.

The patient characteristics are provided in Table 1. Notably, the majority of patients are male (91.1%) and white (94.1%). Most patients had either a base of tongue (51.5%) or tonsil (44.0%) primary, and tended to be former (41.6%) or current (18.8%) smokers. HPV status was available only for 25.7% of patients.

Tumor and Nodal Growth Velocities

The median time between scans was 27 days (range 14–137 days). A total of 202 imaging exams were segmented. Contrast enhanced CT was used in 68% and PET-CT was used in 32% of the segmented images. Excluding patients without radiographically visible primary disease, the median primary tumor volume was 9.6 cc (range 1.1–77.3 cc) on the first scan and 13.4 cc (range 1.3–5.3cc) on the second scan. Median linear TGV was 0.05 cc/day (range 0–0.99 cc/day), which corresponded to a median TGV percentage change of 0.65%/day (range 0–9.37%/day). Two patients had no change in gross tumor volume size. The median volumetric doubling time (t_D) was 112 days (IQR 61–266 days).

Excluding patients without radiographically visible nodal disease, median nodal volume was 11.8 cc (range 1–58.5 cc) on the first scan, and 14 cc (range 0–75 cc) on the second scan. Median linear NGV was 0.07 cc/day (range –0.32–1.22 cc/day), which corresponded to a median NGV percentage change of 0.59%/day (range –.33–5.89%/day). Eleven patients had interval shrinkage of nodes despite no treatment, and three patients had no nodal size change. Figure 1 depicts an example of volumetric changes in primary tumor and nodal targets in the second pretreatment scan compared to the initial scan.

TGV and Treatment Outcomes

Of the 101 patients, 26 (25.7%) had recurrent disease. 10 patients (9.9%) experienced local recurrence, 8 (7.9%) experienced regional recurrence, and 15 (14.9%) developed distant metastases. 26 patients (25.7%) were deceased at the time of review.

Recursive partitioning analysis identified a daily TGV percentage increase associated with local recurrence of 1% per day (7% per week) which corresponded to t_D of 80 days. There was no significant association between TGV and the initial pretreatment tumor volume. Figure 2 demonstrates that patients with TGV $\geq 1\%$ per day had non-statistically different initial tumor volume compared with patients with slower tumor growth with numerically lower mean volume in the TGV $\geq 1\%$ per day compared with the TGV $< 1\%$ per day group (11.6 vs. 14.2 cc, $p=0.3$)

Patients with TGV $\geq 1\%$ per day ($t_D < 80$ days, $n=35$) had 5-year local control rates of 73 %, whereas patients with lower TGV ($n=58$) had 5-year local control rates of 98% ($p = 0.0004$). Figure 3 shows the Kaplan-Meier curve for local control with patients stratified into these two cohorts. Patients with higher TGV also had a 5-year distant-metastasis free survival of

62% as compared to 91% in patients with lower TGV ($p = 0.0007$). Figure 4 depicts the Kaplan-Meier curve for distant-metastasis free survival.

Figure 5 depicts the Kaplan-Meier curve for overall survival. Patients with higher TGV had 5-year overall survival of only 38%, as compared to those with lower TGV, who had 5-year survival of 93% ($p < 0.0001$). Univariate analysis showed that higher TGV was associated with worse local control (HR 16.9; 95% CI 3.1–314.2, $p = 0.0004$), distant-metastasis free survival (HR 5.24; 95% CI 1.9–16.9, $p = 0.002$), and overall survival (HR 10.1; 95% CI 4.03–30.4, $p < 0.0001$).

In multivariate analysis including age, gender, ethnicity, T stage (early T1–2 versus advanced T3–4), smoking status, subsite, pretreatment primary tumor volume, dose, whether the patient received chemoradiation, and whether the patient received induction chemotherapy, TGV 1% per day was the only significant predictor of local control (HR 38.9; 95% CI 3.4–2199.2, $p = 0.02$).

In multivariate analysis examining all these variables as well as N stage, TGV 1% per day was the strongest independent predictor of the development of distant metastases (HR 6.9; 95% CI 2.0–27.3, $p = 0.003$). Smoking status was the only other significant independent predictor ($p = 0.04$). In multivariate analysis examining all the above variables (including N stage), TGV 1% per day was also the strongest independent predictor of overall survival (HR 17.2; 95% CI 5.0–75, $p < 0.0001$). The other significant independent predictors of overall survival was smoking status ($p = 0.0008$). The univariate and multivariate analysis of overall survival is presented in Table 2.

TGV and HPV-status

We also examined patients who were known to be HPV-positive ($n=18$) as well as patients who are never smokers with tonsillar or base of tongue primaries ($n=33$). For this subset of patients ($n=51$) who are presumed as HPV associated, TGV was not significantly associated with local control, development of distant metastases, or overall survival ($P>0.05$ for all).

NGV and Treatment Outcomes

Of the 84 patients with radiographically visible nodal disease and no nodal excision, 73 patients (86.9%) had cystic nodes. In univariate analyses, NGV was not found to be significantly associated with regional control or overall survival. Higher NGV was, however, found to be significantly associated with development of distant metastases (RR 1.62; 95% CI 1.02–2.39, $p = 0.04$).

Discussion

This study suggests that the calculation of tumor growth velocity from serial pre-treatment scans has prognostic value and significantly predicts local control, development of distant metastases, and overall survival. Many patients undergo repeated pretreatment CT scans as part of their oncologic diagnosis, staging, and radiotherapy planning, so incorporation of tumor growth velocity calculations may not require a significant increase in imaging of patients. At our institution, non-contrast CT scans are used for treatment planning in many

cases and so many patients whose records were reviewed were excluded from this study because they did not have two pretreatment contrast CT scans. However, the study results would be applicable for other institutions where both diagnostic and planning CT scans are more likely to be contrast-enhanced. At the same time, incorporation of this strategy would likely have a low time cost, given the relative simplicity of segmenting primary tumor targets for experienced head and neck radiation oncologists.

Our results showed that TGV above the cutoff of 1% increase per day, which is equal to volumetric tumor doubling time of 80 days, was significantly associated with higher risk of local recurrence, development of distant metastases, and death. In contrast, NGV did not appear to be significantly associated with regional recurrence, or overall survival, though was associated with a higher risk of distant recurrence.

Many investigators have examined the prognostic impact of pretreatment CT tumor *volume* as compared to tumor stage in oropharyngeal cancer, and found no significant association between tumor volume and local control in patients treated with radiotherapy^{5,8} or surgery⁷, although some did find a significant association between T stage and local control. Hermans et al. found a significant correlation between tumor volume and local recurrence, but only for T1 tumors.⁶ Ohnishi et al. looked at both OSCC and hypopharyngeal squamous cell carcinoma, and found that pretreatment tumor volume was the most sensitive predictor of local control after radiotherapy, but also found T stage to be significant in multivariate analysis.¹⁰ Meanwhile, Nixon et al. found pathologic tumor volume to be more significantly associated with local and distant control and survival than pathologic T stage, but it is difficult to correlate these findings with imaging estimates given the effects of pathologic fixation and specimen drying after surgery.^{2,9}

In our study, there was no significant correlation between pretreatment tumor volume and TGV. In addition, TGV $\geq 1\%$ per day was the only independent predictor of local control in multivariate analysis including T stage and pretreatment tumor volume. It was also the strongest independent predictor of the development of distant metastases, while neither T stage nor pretreatment tumor volume were significantly associated with distant control in multivariate analysis. In addition, T stage and pretreatment tumor volume were not found to be significant independent predictors of overall survival. However, TGV $\geq 1\%$ per day was a strong independent predictor of overall survival in this analysis.

Only one other study has examined the prognostic impact of tumor growth velocity as opposed to tumor volume. This study, published by Chu et al., examined metabolic tumor velocity (MTV) calculated from metabolic tumor volumes on two pretreatment PET-CT scans. The metabolic tumor volumes were defined as the tumor volume that was greater than or equal to 50% of maximum standardized uptake value. They found that increased MTV significantly predicted risk of disease progression, cancer-specific mortality, and overall risk of death.¹⁴

As in our study, Chu et al. did not find that metabolic nodal velocity was significantly correlated with outcomes. In our study, there was a surprising non-significant trend of NGV above the cut point of 0.6% increase per day correlating with a lower risk of regional

recurrence. Several patients also had interval shrinkage of nodes despite no treatment. The majority of patients in this study had cystic nodes, and one potential hypothesis is that a high NGV cutoff captures patients with rapidly growing cystic nodes, who have an inflammatory reaction to nodal spread of cancer that ultimately results in improved regional control. However, this is speculative at this point and requires further study.

Of note, Chu et al. did find the counterintuitive result of variability in whether the metabolic activity of primary tumors increased over time.¹⁴ In our study, all primary tumors remained the same size or grew between consecutive scans. This may be due to the relatively lower reproducibility of PET-CT scans, as they are influenced by technical factors such as timing between injection and scanning, patient factors such as differences in glucose metabolism or diabetes, and tumor-related factors such as necrosis or inflammation after a procedure (e.g. a biopsy).¹⁷ Simple CT scans without PET may be more reproducible as they are less subject to these types of variability.

Notably, volumetric perfusion CT scan assessments of high blood flow have also been found to significantly predict response to chemoradiation in oropharyngeal squamous cell cancers.^{18,19} However, our method is likely more cost-effective and feasible risk stratification method than usage of PET-CT or perfusion CT, as it would not require repeat or specialized scans, as it is likely reproducible enough to rely upon routine scans that may even have occurred at different institutions.

In the study by Chu et al., there was no correlation between p16 status and MTV, suggesting that HPV status may not be a confounder.¹⁴ However, we also performed an analysis of patients that were known to have HPV-positive cancers or who were never smokers with tonsillar or base of tongue primaries, which are more frequently HPV-positive.²⁰ In these patients, TGV = 1% per day was not significantly associated with local control, development of distant metastases, or overall survival. The significance of this finding is limited, however, by both small size and the assumption of increased HPV-negativity in this subset, and requires studies of patients with known HPV status for validation.

Technical limitations in CT scan differences also exist. Tumor volume calculations performed according to our methodology are generally believed to be within 10–20% of true tumor volume as previously demonstrated in several prior publications.^{2,7,21,22} Recently, Caldas-Magalhaes et al demonstrated that GTVs delineated on CT for laryngeal and hypopharyngeal cancer were 1.7 times larger than the tumor measured on the Hematoxylin-eosin stained pathological sections of the same tumor after surgical resection and registration the respective CT delineations.²³ Also, the first scan utilized could be acquired at an outside hospital with different scanner and different slice thickness than the second scan, which was always done at MD Anderson. This difference may result in error in estimation of comparative tumor volumes. At the same time, there is also inter-observer as well as intra-observer variability that occurs when contouring tumor volumes, as well as variability that may occur in tumors contoured on PET-CT scans.^{24,25} Additionally, MRI-based staging is also becoming more common, which may improve the accuracy of delineation of tumor growth volume because of the superior soft tissue contrast of MRIs over CT scans.²⁶ Also with the introduction of novel treatment devices like MR-Linear accelerators, we will have

further opportunities to interrogate both tumor growth as well as tumor response kinetics in more granular and accurate manner.²⁷ Despite this, at the moment, many patients still receive multiple pretreatment CT scans and the results of this study suggest that TGV calculated from serial pretreatment CT scans, represent a promising tool for risk stratification and outcomes prediction.

Additional limitations are introduced by the retrospective design and relatively small sample of patients that were analyzed. Furthermore, variabilities in patterns of tumor volume growth velocity over time may be introduced. Dependent on changes in the cellular composition of the tumor or transient changes in the tumor microenvironment, such as oxygenation, immune infiltration, or acidity, tumor growth velocity may not be constant. It is possible that measurements over very short time periods may introduce errors, which could be averaged out if images are taken temporary further apart. To our knowledge, no study that conclusively answers if an impact of time on the variation in calculated TGV exists. To decipher patterns of TGV change over time frequent longitudinal radiological scans of untreated tumor growth are required, which is not feasible in current clinical practice. However, we believe that temporal TGV variations will not be observable over the measured entire tumor volume. If such variations do exist, they are likely below the noise level of the variation in tumor volume delineation.

Despite these limitations, evaluation of TGV could potentially enable targeted screening and treatment approaches. Treatment de-escalation with lowered radiation dosages or radiation without concurrent chemotherapy could be explored for patients with low TGV. For patients with high TGV, more aggressive multimodality therapy, such as with induction chemotherapy, could be used for patients who may have early-stage disease but high TGV. At the same time, more frequent imaging surveillance could be done for patients with high TGV, who are at significantly higher risk of both local recurrence and development of distant metastases. Additionally, those patients may be eligible for future dose painting studies or trials of newer agents (e.g. immune checkpoint modulators).

Conclusions and Relevance

Faster TGV is a substantive negative correlate for local control, distant metastasis-free survival, and overall survival in oropharyngeal cancer patients particularly in non-HPV associated tumors. This novel quantitative CT-based volumetric analysis is a simple prognostic tool that demarcates a high-risk group for which treatment and screening strategies could be optimized. Future efforts are needed to validate our findings in independent datasets.

Acknowledgments

Dr. Fuller received/receives grant and/or salary support from: the National Institutes of Health (NIH)/National Institute for Dental and Craniofacial Research (1R01DE025248-01/R56DE025248-01), the NIH/National Cancer Institute (NCI) Head and Neck Specialized Programs of Research Excellence (SPORE) Developmental Research Program Award (P50CA097007-10) and Paul Calabresi Clinical Oncology Program Award (K12 CA088084-06); a National Science Foundation (NSF), Division of Mathematical Sciences, Joint NIH/NSF Initiative on Quantitative Approaches to Biomedical Big Data (QuBBB) Grant (NSF 1557679); a General Electric Healthcare/MD Anderson Center for Advanced Biomedical Imaging In-Kind Award; an Elekta AB/MD Anderson Department of Radiation

Oncology Seed Grant; the Center for Radiation Oncology Research (CROR) at MD Anderson Cancer Center; and the MD Anderson Institutional Research Grant (IRG) Program.

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Highlights

- CT-based volumetric assessment of oropharyngeal tumor growth velocity is proposed.
- Velocity is calculated from pretreatment scans with time gap of more than 2 weeks.
- Velocity $\geq 1\%$ per day is predictive of worsened disease control and survival.
- In presumed HPV-related tumors, higher velocity is not predictive of outcomes.
- Higher nodal growth velocity is associated with distant metastases.

Time point 1

Time point 2

Figure 1.

Sample Tumor and Nodal Growth on Pretreatment CT Scans. An example of primary tumor and nodal target volumetric changes in the later pretreatment scans (dotted contour) compared with the initial scan (solid contour).

Figure 2.

Pretreatment Tumor Volume by Tumor Growth Velocity (TGV) Group. Pretreatment tumor volumes are not significantly different in patients with TGV ≥ 1% per day and those with TGV < 1% per day.

Figure 3. Local Control by Tumor Growth Velocity (TGV) Group. Kaplan-Meier curve showing local control (in months) for patients with TGV < 1% per day and TGV ≥ 1% per day.

Figure 4. Distant Control by Tumor Growth Velocity (TGV) Group. Kaplan-Meier curve showing distant-metastasis free survival (in months) for patients with TGV < 1% per day and TGV 1% per day.

Figure 5. Overall Survival by Tumor Growth Velocity (TGV) Group. Kaplan-Meier curve showing overall survival (in months) for patients with TGV < 1% per day and TGV ≥ 1% per day.

Table 1

Patient Characteristics

Characteristics	n (%)
Sex	
F	9 (8.9%)
M	92 (91.1%)
Age, y: median (range)	61 (36–89)
Ethnicity	
White	95 (94.1%)
Black	2 (2.0%)
Hispanic	4 (4.0%)
Site	
Base of tongue	52 (51.5%)
Tonsil	44 (44.0%)
Soft palate	2 (2.0%)
Lateral pharyngeal wall	2 (2.0%)
T stage	
T1	8 (7.9%)
T2	41 (40.6%)
T3	30 (29.7%)
T4	19 (18.8%)
TX	2 (2.0%)
N stage	
N0	11 (10.9%)
N1	8 (8.0%)
N2	71 (70.3%)
N3	8 (7.9%)
NX	3 (3.0%)
Karnofsky performance status	
60	1 (1.3%)
70	10 (12.7%)
80	28 (35.4%)
90	34 (43.0%)
100	6 (7.6%)
Missing	22 (21.8%)
Smoking	
Former	42 (41.6%)
Current	19 (18.8%)
Never	40 (39.6%)
HPV	
Positive	18 (17.8%)
Negative	8 (7.9%)

Characteristics	n (%)
Unknown	75 (74.3%)

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Table 2

Results from univariate and multivariate regression analyses

Characteristics	Univariate			Multivariate		
	HR (95% CI)	P		HR (95% CI)	P	
Age	Continuous variable	-	0.8	-	-	0.6
Sex	Male	1		1		
	Female	0.3 (0.1–1.6)	0.3	0.4 (0.1–10.5)		0.5
Race	Caucasian	1		1		
	Others	2.9 (0.7–8.4)	0.08	1.1 (0.1–5.1)		0.9
Site	Tonsil	1	1			
	Base of tongue	0.8 (0.3–1.7)	0.5	1.2 (0.2–6.3)		0.8
	Others	1.3 (0.7–6.7)	0.8	10.1 (0.3–282)		0.2
T stage	T1–T2	1		-		
	T3–T4	2.2 (0.97–5.1)	0.057	1.8 (0.4–8.5)		0.4
N stage	N0–N1	1		1		
	N1–3	0.9 (0.4–2.7)	0.8	0.7 (0.1–5.3)		0.7
Smoking status	Never	1		1		
	Former	2 (0.7–7.5)	0.2	4.3 (0.9–32.4)		0.07
	Current	8.7 (3–31)	0.0001*	11.9 (2.7–85.5)		0.0008*
Radiation dose	Continuous variable	-	0.2	-		0.9
Concurrent chemotherapy	No	1		1		
	Yes	1.3 (0.6–3.6)	0.5	0.2 (0.1–1.9)		0.2
Induction chemotherapy	No	1		1		
	Yes	1.4 (0.6–3.3)	0.4	1.2 (0.2–9)		0.8
Pretreatment tumor volume (cc)	Continuous variable	-	0.06	-		0.2

Characteristics	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Pretreatment nodal volume (cc)	-	0.6	-	0.6
Tumor growth velocity	<1% per day 1% per day	1	17.2 (5–75)	0.0001*