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Prognostic impact of tumor growth velocity in head and neck squamous cell carcinoma treated by radiotherapy: A pilot study

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Abstract

Background: When a patient is seen with a newly diagnosed oropharyngeal squamous cell carcinoma, it remains unclear to the treating physicians how fast the tumor growth rate is.

Methods: From patients with oropharynx squamous cell carcinoma treated by radiotherapy, the investigators selected comparable diagnostic CT-scan (DiCT) and radiotherapy planning CT-scan (RtCT). Tumor and pathological lymph node volumes were measured in order to calculate tumor progression.

Results: From the selection of 19 patients, the mean absolute tumor progression rate was 0.23 ± 0.2 cm^3/d and mean relative progression rate was 1.84 ± 1.64%/d. Mean tumor doubling time is 286 days (range 7-1282 days), demonstrating a wide range of tumor growth pattern. Significant tumor progression (>20%) between DiCT and RtCT was shown in 73% of patients, and 53% of the patients were seen a tumor progression of >50% within a mean waiting time of 42.1 days. Kaplan-Meier curves showed a non-significative link between fast progression tumors (>1%/d) and higher risk of recurrence (HR: 2.2; $P = .23$).

Conclusions: Tumor progression can be assessed based on DiCT and RtCT. Treatment delay should be avoided at all cost. Different growth patterns were evidenced. For the fast-growing tumors subgroup, pejorative clinical outcomes were suggested. Prospective studies are needed to confirm a link between fast-growing tumors and higher risk for recurrence.

KEYWORDS
oropharynx carcinomas, progression, tumor growth

1 | INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) represents more than 90% of head and neck tumors and is one of the most frequent human neoplasms. Oropharynx squamous cell carcinoma (OPSCC) has emerged as one of the most common malignancies in the head and neck sites. Around 123 000 new cases of oropharyngeal cancers are estimated to occur annually worldwide, resulting in 79 000 annual deaths.[1] Significant progress has been made in the understanding of the development and progression of OPSCC, but they often remain unpredictable at the time of diagnosis.

During the last decades, radiotherapy has emerged as a standard treatment of HNSCC and the number of patients treated with this modality has continuously increased. Moreover, treatment schedules for radiotherapy have improved but require more preparation and are therefore more time consuming.[2] Increasing waiting time prior to radiotherapy has

become of major concern in many countries with reported delays rising up to 70 days.[3] Brouha et al[4] already reported a median time period of 43 days between the date of histopathological diagnosis and the beginning of radiotherapy for patients with T1N0M0 glottic laryngeal carcinoma.

Radiologic assessment of the OPSCC tumor should include at least a contrast enhanced CT scan. After complete assessment and staging, for patients addressed for radiation therapy, a second CT scan will be performed several weeks later for treatment planning in order to define the tumor target volume. This necessity provides the opportunity to compare tumor volumes on both exams, and therefore to assess tumor progression.

Correlation between tumor size and treatment response is known for patients with head and neck cancers.[5-7] It is also well documented that the local control probability is related to nodal status and to the volume of metastatic nodes.[8-10]

In the present study, we studied retrospectively the tumor and locoregional progression in the waiting time between diagnostic and treatment planning CT scans in a cohort of patients with OPSCC, treated by radio(chemo)therapy between April 2005 and April 2007. Tumor and node volumes were measured on comparable CT scans in order to evaluate the tumor progression during the delay for radiotherapy and calculate tumor doubling time (TDT). Patients' clinical outcomes were studied in order to determine if the tumor progression can be used as a prognostic factor.

2 | PATIENTS AND METHODS

2.1 | Patients

All patients with an oropharyngeal primary squamous cell carcinoma treated by radiotherapy or chemoradiation with curative intent in radiotherapy department of Institut Gustave Roussy from April 2005 to April 2007 were identified. Patients with metastatic disease or with previous history of previous head and neck carcinomas were excluded. One hundred seventeen patients were collected; 27 patients were finally treated in other centers, 35 patients had no digitalized CT scans, and 19 patients had CT scans with no contrast injection. From the remaining 36 patients, we excluded all cases with MRI or CT-scans on which a valid tumor volume measurement or comparison on both exams could not be assessed. Finally, 19 patients were selected with comparable diagnostic CT scan and treatment planning CT scan. Follow-up data were retrieved for all selected patient.

2.2 | Radiological technique and tumor progression evaluation

Tumor volume was calculated for each patient on the diagnostic CT and the treatment planning CT. Tumor volume, number, and size of pathological cervical lymph nodes were assessed on both exams and classified according to the 2007 American Joint Committee on Cancer (AJCC) classification. The volume of cervical lymph nodes considered as positive (small diameter >1 cm and/or necrotic center) were calculated using the same method. Diagnostic CT scans have an inter-slice distance of 2 mm and a slice thickness of 3 mm whereas pretreatment CT scans have an inter-slice distance of 3 or 5 mm with a similar slice thickness of 3 or 5 mm. Contrast infusion was given in all cases.

Tumor volume was assessed using the summation of areas technique: tumor area was manually outlined on each CT slice and tumor volume was calculated by multiplying each cross-sectional area by inter-slice distance and adding slices together (Figure 1). Two different observers validated these data using Dosisoft Isogray software (1 radiotherapist and 1 surgeon).

2.3 | Statistical analysis

For each patient, the volumes of the tumor recovered from the treatment planning CT and from the diagnostic CT and the waiting time (ie, the time between both CTs) were used to compute several statistics including the absolute volume increase (cm^3), the relative volume increase (%), the absolute volume increase rate (cm^3/d), the relative increase rate (%/d), and the TDT (day). TDT evaluation was based on progression of primary tumor only. Twenty percent of relative tumor increase was considered as progression threshold.

Overall and disease-specific survival time were computed for each patient as the time between the diagnostic CT until death (all causes or restricted to oropharyngeal primary squamous cell carcinoma, respectively) and were censored at last follow-up for patients remaining alive. Disease-specific and relapse-free survival time were computed for each patient as the time between the diagnostic CT until first relapse or death and were censored at last follow-up for patients remaining alive and without any relapse.

All patients (n = 19) were separated into two groups according to the relative tumor increase rate (slow progression rate: <1%/d [n = 10] vs fast progression rate: >1%/d [n = 9]).

Kaplan-Meier curves were plotted to compare disease-specific survival and relapse-free (disease specific) survival between patients with slow and fast total tumor (T + N) progression rates. Hazards ratio between both groups were computed using Cox proportional hazards regression models. Statistical significance was set at $P < .05$. All analyses were performed using R statistical software R.3.1.2.

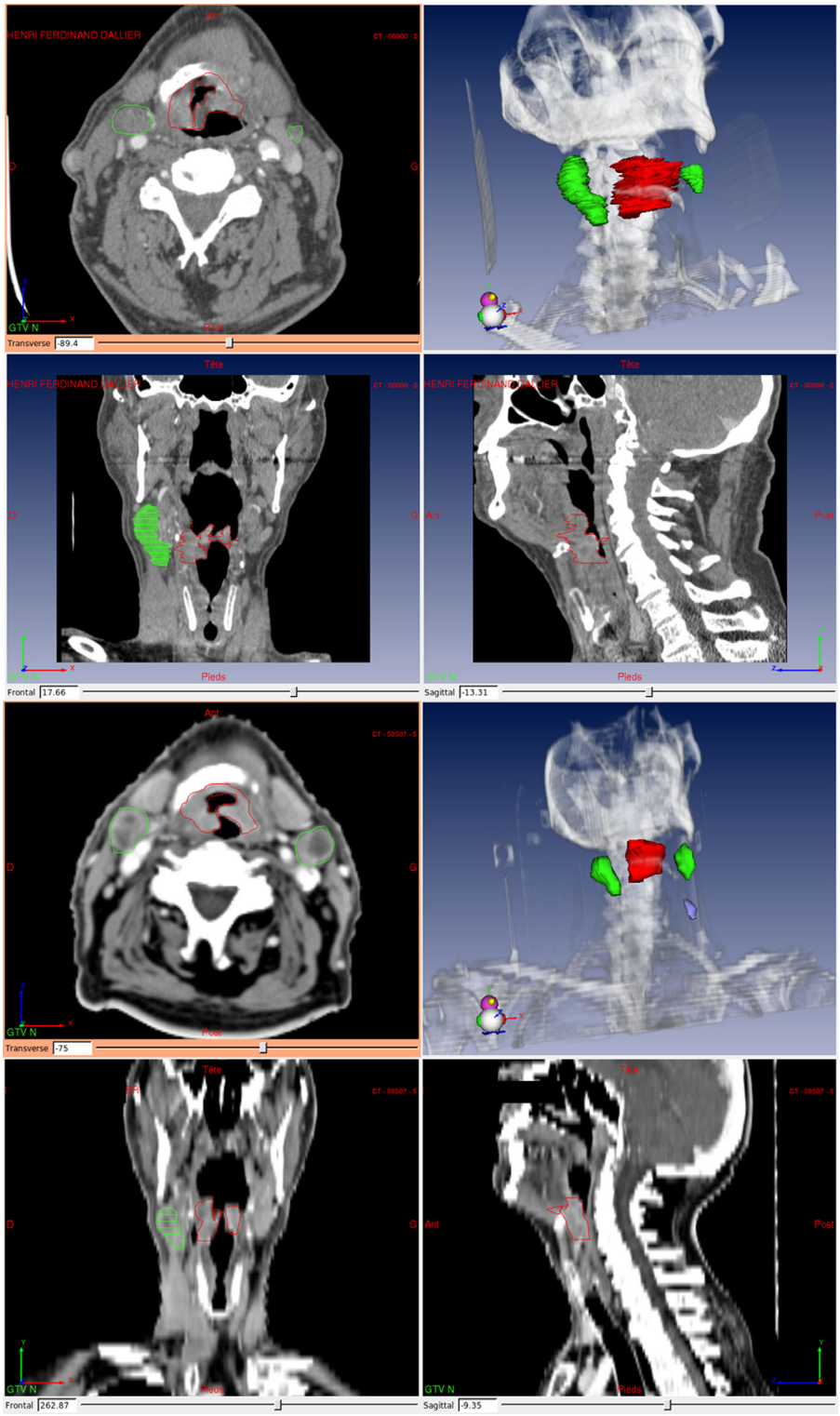

FIGURE 1 Tumor volume assessment. Tumor limit was manually outlined on each CT slice and tumor volume was calculated by multiplying each cross-sectional area by inter-slice distance and adding slices together using Dosisoft Isogray software [Color figure can be viewed at wileyonlinelibrary.com]

3 | RESULTS

One hundred seventeen patients were identified in Gustave Roussy Institut with OPSCCs treated by radiotherapy between April 2005 and April 2007. We identified 19 eligible patients, 14 men and 5 women. Mean delay between diagnostic CT scan and pre-radiotherapy CT was 42 days (from 12 to 72 days).

Table 1 shows total tumor (T + N) volume on diagnostic and pretreatment CT scans, absolute and relative total tumor (T + N) increase, absolute and relative tumor (T) progression, and TDT. Mean absolute volume increase for T was 8.9 cm^3 (min = −0.6 cm^3; max = 34.2 cm^3), corresponding to a relative increase of 56.3% (min = −8%; max = 194%). Mean absolute volume increase for N was 4.4 cm^3 (min = −1.7 cm^3; max = 15 cm^3), corresponding to a relative

TABLE 1 Tumor volume data. Absolute and relative volume increase, absolute and relative tumor progression, and tumor doubling time patient per patient

Patient	Sex	Total volume diagnostic CT (cm^3)	Total volume radiotherapy CT (cm^3)	Absolute total volume increase (cm^3)	Relative total volume increase (%)	Absolute tumoral (T) progression (cm^3/d)	Relative tumoral (T) progression (%/d)	Tumor doubling time (days)
1	M	22.62	23.16	0.54	2.38	0.01	0.07	1282
2	F	21.80	59.88	38.08	174.67	0.95	5.41	18
3	M	10.13	18.29	8.16	80.55	0.16	1.57	63
4	F	27.08	35.81	8.73	32.23	0.10	0.61	162
5	M	1.95	3.22	1.27	65.12	0.02	1.03	96
6	F	5.04	3.63	−1.41	−27.97	0.02	12.91	7
7	M	54.86	71.76	16.90	30.8O	0.15	0.42	237
8	M	24.89	45.98	21.09	84.73	0.45	1.84	54
9	M	9.46	10.06	0.60	6.34	−0.00	−0.23	(1282)
10	F	31.58	50.53	18.95	60.00	0.73	2.66	37
11	M	54.68	89.29	34.61	63.29	0.45	0.99	100
12	M	65.19	98.00	32.81	50.32	0.53	1.08	92
13	M	45.27	62.06	16.79	37.08	0.28	0.99	100
14	M	31.51	41.21	9.70	30.78	0.10	1.99	50
15	M	18.18	28.66	10.48	57.64	0.16	0.89	111
16	M	8.03	12.64	4.61	57.40	0.00	1.62	61
17	F	19.94	34.10	14.16	71.01	0.04	0.86	115
18	M	24.95	27.33	2.38	9.53	−0.01	−0.10	(1282)
19	M	84.22	100.07	15.85	18.81	0.28	0.35	277
Mean				13.38	47.62	0.23	1.84	42
Median				10.48	50.33	0.15	0.99	41

volume increase of 51% (min = −35%; max = 200%). Mean total volume (T + N) absolute increase was 13.3 cm^3 (min = −1.4 cm^3; max = 38 cm^3), corresponding to a relative increase of 47% (min = −27%; max = 174%). Figure 2 shows an example of tumoral progression evaluation. Figure 3 shows the repartition of the population in terms of absolute and relative volume increase for the tumor (T), for the nodes (N), and the total volume (Total).

An average absolute progression rate for tumor volume of 0.23 cm^3 per day (min = −0.01; max = 0.95 cm^3 per day) was computed which corresponded to a mean relative progression rate of 1.84% per day (min = −0.23; max = 12.9%

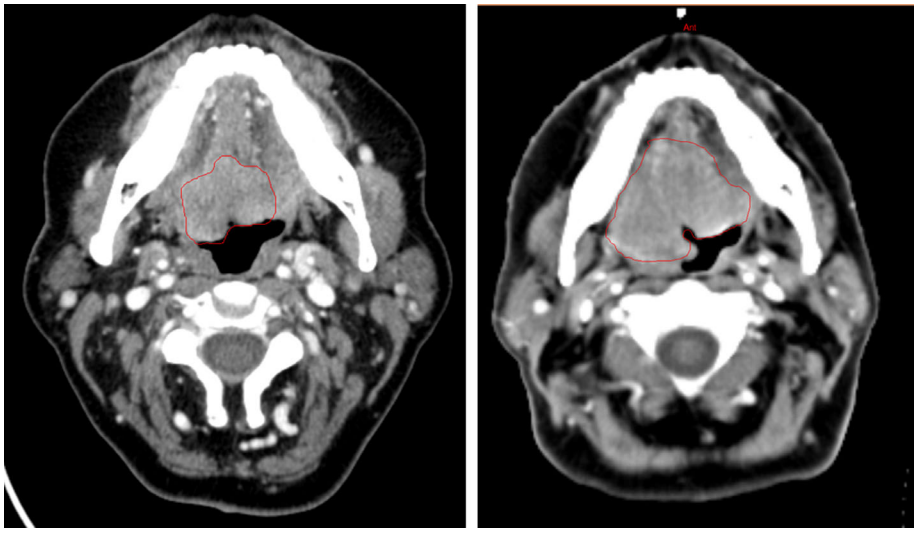

FIGURE 2 Tumor progression evaluation. Based on volumes calculated on diagnostic CT scan and pretreatment scan, and the delay between these two procedures, tumor volume, tumor volume doubling time, and changes in TNM stage are calculated. In this example, the tumor progressed, within 36 days, with a relative volume increase of 174.7%, giving a tumor doubling time of 20.6 days [Color figure can be viewed at wileyonlinelibrary.com]

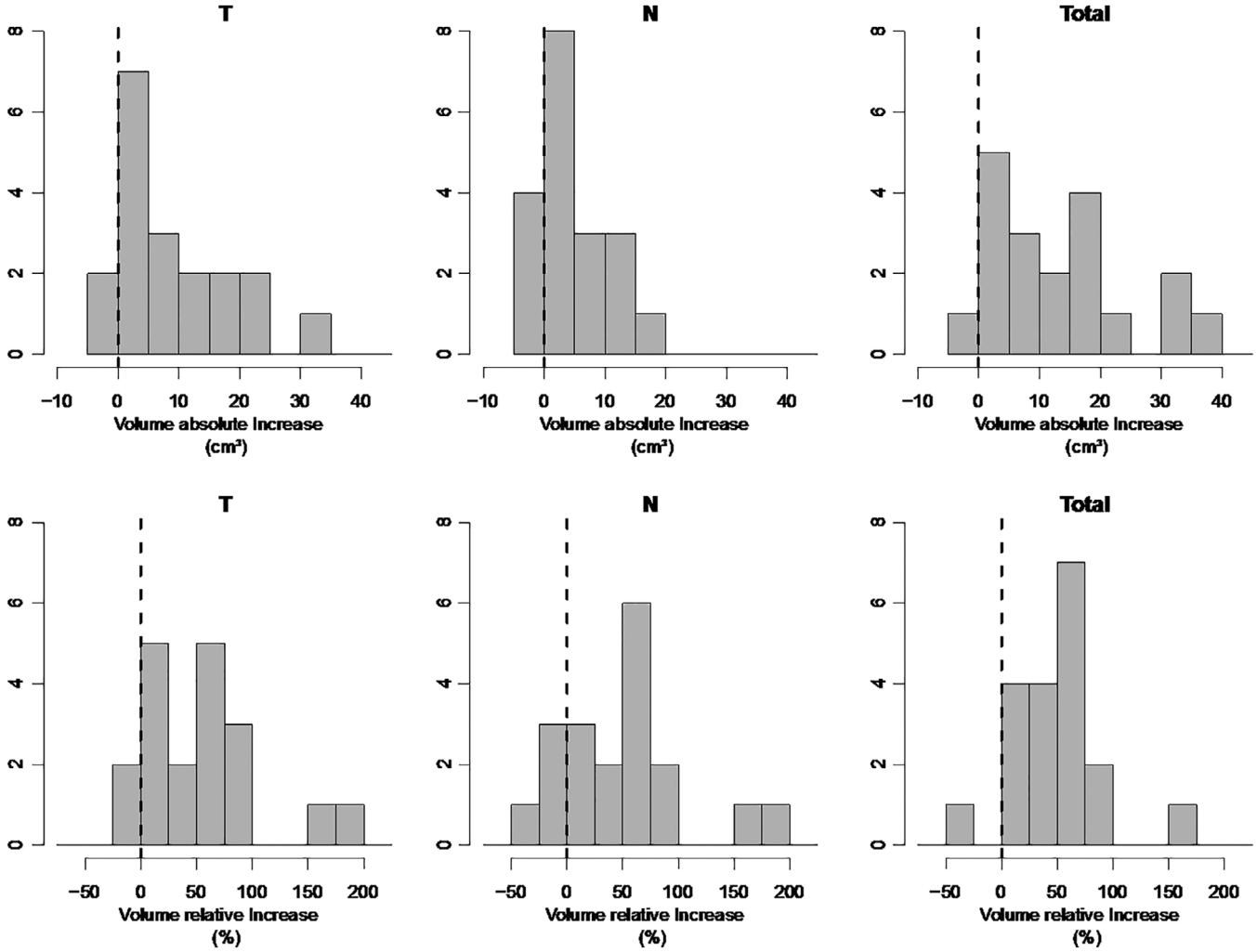

FIGURE 3 Repartition of the population for absolute and relative volume increase for tumor volume (T), node volume (N), and total volume (Total)

per day). Figure 4 shows the repartition of progression rate for our population.

TDT was determined using only T volume increase. Mean TDT was 286 days (min = 7 days; max = 1282 days). Given the right-skewed distribution, a median value of 100 days was computed and considered as more relevant than the corresponding mean, three patients being outliers, as shown in Figure 4. No correlation was found between initial tumor volume and growth rate.

Using RECIST criteria (20% volume progression), 73% of patients showed a significant tumor progression between DiCT and RtCT. Fifty-three percent of the patients presented a tumor progression of >50%. Using AJCC classification, five patients progressed up in TNM classification (Table 2). As shown in Kaplan-Meier curves (Figures 5 and 6), the relapse-free survival and disease-specific survival were impacted by the progression rate of the tumor size. Although these results were not statistically significant ($P = .23$ for relapse-free survival and $P = .21$ for disease-specific survival) due to the particular small sample size (n = 19) of the present pilot study, hazards ratio were however high (HR ~ 2.2) between slow and fast progression rate.

4 | DISCUSSION

Tumor progression can be assessed with good precision, based on diagnostic and pretreatment CT scans and using the summation of areas technique. Common delay between CT scans allows us to study growth velocity.

In this retrospective pilot study, we studied 19 patients with oropharyngeal cancer and observed that tumor progression could be considerable and sizable. Indeed, we showed that 73% of patients showed a significant tumor progression between diagnostic and pretreatment CT scans using RECIST criteria (20% volume progression). The mean delay between diagnostic CT and pre-radiotherapy CT was 42 days (from 12 to 72 days). Tumor growth during this waiting time can potentially decrease treatment results.

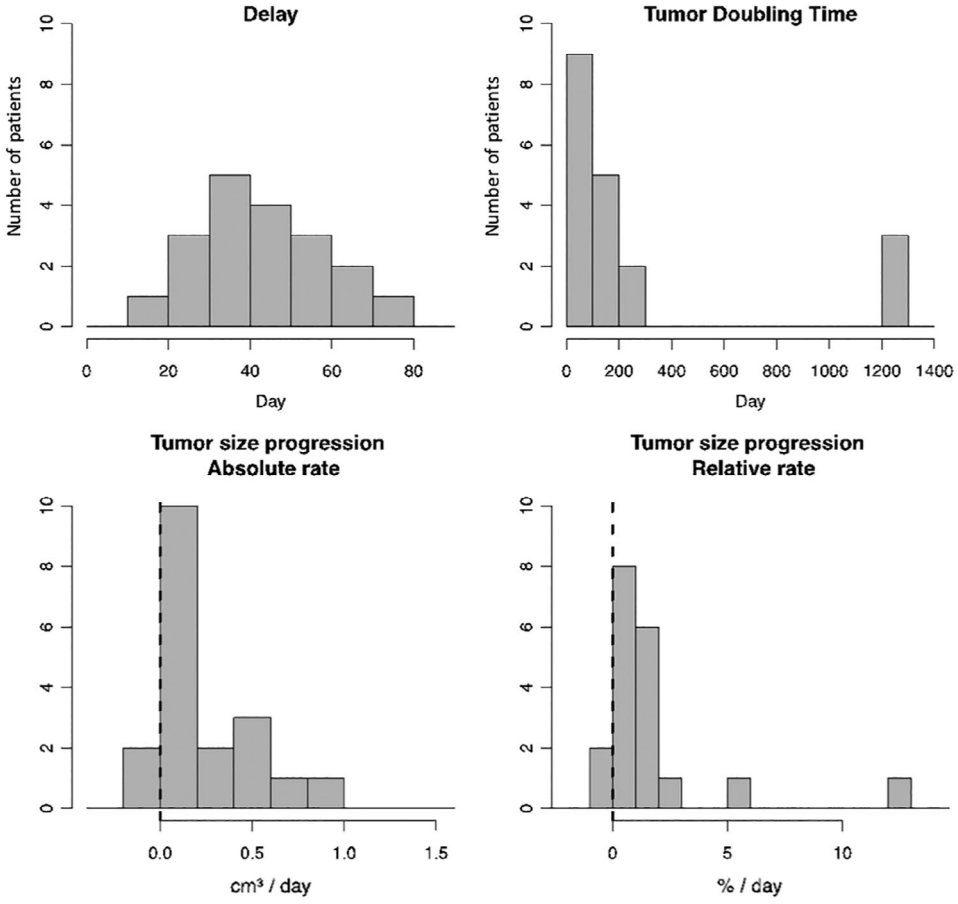

FIGURE 4 Repartition of the population for delay between diagnostic and pretreatment CT scans, tumor doubling time, absolute, and relative tumor progression

TABLE 2 TNM staging and tumor localization: five patients (in bold) were upstaged

Patient	TNM CT1	Tumor localization	TNM CT2
1	T2N2c	Tonsillar fossa	T2N2c
2	**T4aN2c**	**Base of the tongue**	**T4bN2c**
3	**T2N0**	**Base of the tongue**	**T3N0**
4	T4bN2c	Soft palate	T4bN2c
5	T2N0	Base of the tongue	T2N0
6	T1N2b	Base of the tongue	T1N2b
7	T3N2b	Glossoepiglottic fold	T3N2b
8	T4aN0	Posterior pharyngeal wall	T4aN0
9	T1N2c	Soft palate	T1N2c
10	T4aN2b	Base of the tongue	T4aN2b
11	**T4aN1**	**Posterior pharyngeal wall**	**T4aN2a**
12	T4bN2c	Base of the tongue	T4bN2c
13	T4aN2b	Base of the tongue	T4N2b
14	**T2N2b**	**Tonsillar fossa**	**T2N3**
15	**T4bN0**	**Tonsillar fossa**	**T4bN1**
16	T2N2b	Soft palate	T2N2b
17	T2N2c	Vallecula	T2N2c
18	T3N2c	Vallecula	T3N2c
19	T4bN2b	Tonsillar fossa	T4bN2b

Very different tumor kinetics patterns have been demonstrated. A few patients had relatively stable disease and appeared outliers for relative progression rate. Therefore, we used median rate as threshold value to separate our population in slow and fast-growing tumors. Progression rate and TDT were calculated on T volume to focus on primary tumor volume. Considering the absolute and relative total (T + N) volume increase (cm^3), all patients but five showed a tumor progression. Tumor regression was observed in one patient, due to the nodal volume decrease. This result may be explained by an initial inflammatory nodes, by nodal necrosis during the waiting time, or by the limitation of the summation-of-areas technique.

Mean TDT was 286 days. Given the right-skewed distribution, a median value of 100 days was computed which is in line with published data.[2] We found very different kinetic patterns with some tumor volume increase up to 174% and progression of staging in five patients during the time between the diagnostic scan and the pretreatment scan. This is important, taking into account that the real waiting time between diagnosis and treatment is longer because of the additional time between the pretreatment CT scan and the start of radiotherapy. When considering this complete waiting time, we can therefore emphasize that the real increased tumor volume is more important.

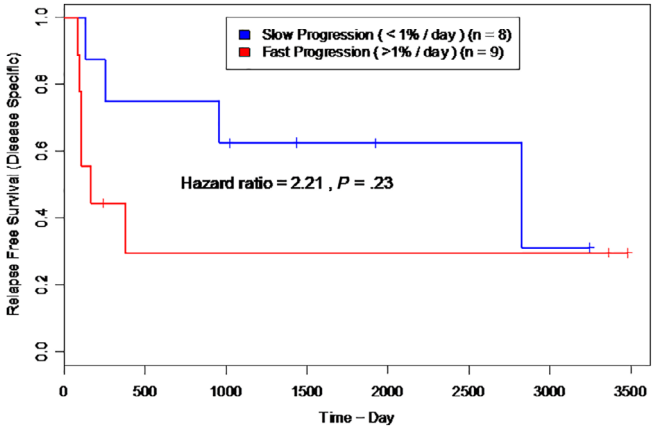

FIGURE 5 Kaplan-Meier curve of recurrence-free survival [Color figure can be viewed at wileyonlinelibrary.com]

Kaplan-Meier curves were calculated with a progression rate calculated on T + N progression rate because node progression has a clinical impact on survival. We found that relapse-free survival and disease-specific survival were impacted by the progression rate of the tumor size. Even if these results were not statistically significant ($P = .23$ for relapse-free survival and $P = .21$ for disease-specific survival), hazards ratio was however high (HR ~ 2.2) between slow and fast-progression rate. Significance was not reached due to the particular small sample size (n = 19) of the present pilot study. However, van Bockel et al[11] studied the importance of tumor growth rate on clinical outcomes in laryngeal squamous cell carcinoma, demonstrating that this tumor growth rate seems to be an important factor in disease-free survival and overall survival.

One hundred seventeen patients were identified but 84% were excluded mainly because of incomparable diagnostic and pretreatment CT scans. According to the publication of Ang et al,[12] human papillomavirus (HPV) status of the OPSCC tumor is a major determinant of overall survival, followed by the number of pack-years of tobacco smoking and then nodal stage for HPV-positive tumors, or tumor stage for HPV-negative tumors. It is clearly suggested for the future clinical trials on OPSCC to stratify HNSCC cohort for HPV status. In the present study, HPV status was not assessed because it is not evaluated systematically at Institut Gustave Roussy in 2005 and histologic specimens are no longer available for this analysis despite our efforts. Although this pilot study demonstrates a wide range of tumor growth patterns, the size of the cohort is not sufficient to clearly conclude on the clinical consequences of the waiting time between diagnostic and pretreatment CT scans. In order to demonstrate its potential consequences on patient clinical outcome, prospective studies with a cohort of patients stratified for HPV status are needed. These different clinical patterns should also be correlated with HPV status, differentiation status, and proliferation markers (Ki67, mitotic index). Further biological markers should be sought to detect fast-growing tumors at the time of diagnosis.

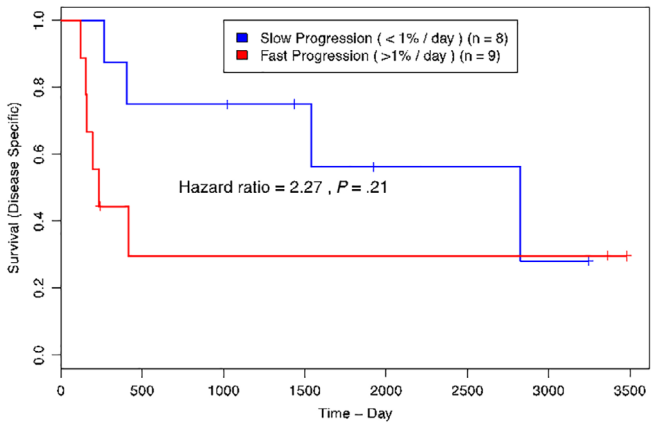

FIGURE 6 Kaplan-Meier curve of disease-specific survival [Color figure can be viewed at wileyonlinelibrary.com]

This retrospective study was initiated as a pilot study to evaluate tumor growth during the waiting time between diagnostic and pretreatment CT scans and to obtain an indication of its clinical consequences. A limitation is the low number of patients that could be included in the study. Nevertheless, this small retrospective study is well-designed and represents an important step in the setup of a good multicentric prospective study. This low informative rate highlights the importance of a strictly designed imaging protocol to ensure an accurate comparison between diagnostic and pretreatment CT scans. It shows the feasibility to evaluate tumor progression rate between diagnostic CT scan and pre-radiotherapy CT scan with tumor delineation software. Different kinetic patterns are demonstrated and correlation with recurrence-free survival is suspected.

Prospective studies with a cohort of patients stratified for HPV status are needed in order to demonstrate the potential significant correlation between the tumor kinetics patterns and the patient clinical outcomes.

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