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Original Article

Early and late contrast enhancing lesions after photon radiotherapy for *IDH* mutated grade 2 diffuse glioma

Jaap P.M. Jaspers [a,d,*], Walter Taal [b], Yvette van Norden [a], Jaap D. Zindler [c,d], Annemarie T. Swaak [a], Steven J.M. Habraken [a,d], Mischa S. Hoogeman [a,d], Remi Nout [a], Martin J. van den Bent [b], Alejandra Méndèz Romero [a,d]

[a] *Department of Radiotherapy;* [b] *Neurology Department, Brain Tumor Center, Erasmus MC Cancer Institute, Erasmus MC University Medical Center, Rotterdam;* [c] *Department of Radiotherapy, Haaglanden Medisch Centrum, Leidschendam; and* [d] *Holland Proton Therapy Center, Delft, the Netherlands*

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ABSTRACT

Objective: The interpretation of new enhancing lesions after radiotherapy for diffuse glioma remains a clinical challenge. We sought to characterize and classify new contrast enhancing lesions in a historical multicenter cohort of patients with IDH mutated grade 2 diffuse glioma treated with photon therapy.
Methods: We reviewed all follow-up MRI's of all patients treated with radiotherapy for histologically confirmed, IDH mutated diffuse grade 2 glioma between 1–1-2007 and 31–12-2018 in two tertiary referral centers. Disease progression (PD) was defined in accordance with the RANO criteria for progressive disease in low grade glioma. Pseudoprogression (psPD) was defined as any transient contrast-enhancing lesion between the end of radiotherapy and PD, or any new contrast-enhancing lesion that remained stable over a period of 12 months in patients who did not exhibit PD.
Results: A total of 860 MRI's of 106 patients were reviewed. psPD was identified in 24 patients (23%) on 76 MRI's. The cumulative incidence of psPD was 13% at 1 year, 22% at 5 years, and 28% at 10 years. The mean of the observed maximal volume of psPD was 2.4 cc. The median Dmin in psPD lesions was 50.1 Gy. The presence of an 1p/19q codeletion was associated with an increased risk of psPD (subhazard ratio 2.34, p = 0.048). psPD was asymptomatic in 83% of patients.
Conclusion: The cumulative incidence of psPD in grade 2 diffuse glioma increases over time. Consensus regarding event definition and statistical analysis is needed for comparisons between series investigating psPD.

The development of new contrast-enhancing lesions on MRI imaging after radiotherapy that are not indicative of disease progression (PD), was first described as pseudoprogression (psPD) in high grade gliomas [1,2]. Later published work confirmed the occurrence of psPD after radiotherapy for adult grade 2 and 3 diffuse gliomas. With the median progression free survival for grade 2 diffuse gliomas exceeding 10 years after radiotherapy and adjuvant chemotherapy, the likelihood of encountering some form of psPD during follow-up is substantial, with a reported prevalence of 18 to 35% [3–10].

Although often asymptomatic, the recognition of psPD is important in both clinical care and in the definition of scientific endpoints. As treatment decisions are often based on MRI follow-up, misjudgment of psPD as PD could lead to premature initiation of a new line of treatment. The risk of psPD interfering with endpoint definition in clinical trials was addressed in the 2017 update of the Response Assessment in Neuro-Oncology (RANO) criteria [11]. Both early and delayed presentations of psPD are known to occur [12].

Recently, psPD has become of interest as an adverse effect of proton beam therapy (PT) for diffuse glioma [13]. Although PT allows for a more compact dose distribution compared to photon beam therapy (XRT), the relative biological effectiveness of proton dose distributions is still subject of debate [14,15]. In this regard, psPD has been studied as a potential biomarker for the biological effect of PT in the central nervous system [16,17]. Although the two studies that report the highest prevalence of psPD in grade 2 glioma concerned PT treatments [8,10], an informed comparison of the risk of developing psPD after PT versus XRT would require information on the incidence of psPD over time.

In this work, we describe psPD based on onset, duration, size, location, and dose delivered in a cohort of patients with *IDH*

* Corresponding author at: Department of Radiotherapy, Erasmus MC Cancer Institute, Erasmus MC University Medical Center, Doctor Molewaterplein 40, 3015 GD Rotterdam, the Netherlands.
E-mail address: j.jaspers@erasmusmc.nl (J.P.M. Jaspers).

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mutated diffuse glioma treated with XRT. Using survival analysis allows for estimating the incidence of psPD over time, the relationship between psPD and survival, and comparisons of the risk of psPD between subgroups of grade 2 diffuse glioma patients.

Methods

The study was conducted according to the principles of the Declaration of Helsinki (59th WMA General Assembly, Seoul, October 2008) and in accordance with the local medical research regulations. The study protocol was presented to the local Medical Ethics Committee (MEC-2020–0604) of Erasmus MC and Haaglanden MC and considered not subject to the Medical Research Involving Human Subjects Act.

We reviewed the charts of all patients with histologically confirmed, *IDH* mutated grade 2 diffuse glioma treated with XRT between 1–1-2007 and 31–12-2018 in Erasmus MC and Haaglanden MC, both tertiary centers. Resection status was defined as either biopsy or any other resection grade. Radiotherapy treatment was prescribed according to ICRU 50 and delivered using 3DCRT or IMRT techniques available at the time. Typical treatment volumes comprised a GTV that includes the resection cavity and T2/FLAIR abnormalities, a CTV expansion of 10 – 15 mm, and a PTV expansion of 5 mm.

We defined PD by retrospectively applying the RANO criteria to the lesion that was eventually identified as disease recurrence by the multidisciplinary tumor board as described before [18]. The date of PD was defined as the date of the first MRI that satisfied the RANO criteria for disease progression. A new contrast enhancing lesion was defined as psPD if it vanished during follow-up, or remained stable over a period of at least 12 months without treatment, as defined by van West et al [4]. Contrast enhancing lesions that were already visible on pre-radiotherapy imaging were not defined as psPD.

All MRI scans between end of radiotherapy and PD were reviewed by one author (JJ) for contrast enhancing lesions. The procedure of reviewing each MRI included revision of the T1 weighted and T1 weighed contrast enhanced (T1gad) images. These were correlated with T2 weighted images when needed. MRI scans that showed one or more contrast enhancing lesions were reviewed by three authors (AMR, WT, JJ). The interpretation of each lesion was discussed until consensus was reached. In patients with transient lesions, duration of psPD was defined as the time interval between the first MRI that showed psPD to the first MRI that showed resolution of psPD.

For all cases with psPD, we retrieved the complete original radiotherapy planning data. The T1gad series of each MRI that showed psPD was rigidly registered to the original planning CT using MIM (MIM software, version 7.1.6, Cleveland, Ohio). Next, each lesion was delineated manually on each MRI. In line with the analysis of Bahn et al [16], we defined the ventricular fringe (VF) as a 4 mm expansion of the ventricles. For the psPD volumes, the GTV and the VF, overlap was defined as an overlap of one or more voxels. DVHs were generated for the cumulative psPD volume at each time point. Additionally, for each MRI that showed psPD, the medical records of the associated clinical visit were scored by three authors (AMR, WT, JJ) as either "asymptomatic" or "symptomatic" based on reported neurological status or clinical performance score. Again, interpretation of records was discussed until consensus was reached.

Descriptive statistics were generated for all variables. Next, psPD is analyzed as a time-to-event outcome in presence of competing events. To this effect, a series of Cox regression models were generated: one for overall survival (OS), one for progression free survival (PFS) and one for "pseudo-progression free survival" (psPDFS). For PFS both death from all causes and PD are considered competing failures. psPDFS is defined as the time from end of RT to death from all causes, PD or psPD, whichever comes first. These are used to provide estimates of event free survival, as well as well as estimating the relative effect of covariates on the cumulative incidences. In order to investigate the relationship between covariates and the distribution of the subhazards death from all causes, PD and psPD within psPDFS, a Fine and Gray model was generated. This model can be used to investigate the effect of covariates on the incidence of the psPD [19].

In order to compare OS between the group of patients with and without psPD a separate Cox regression model was generated using psPD as a time-dependent covariate. Additionally, a Simon-Markuch plot was generated. Finally, time effects on lesion volume were assessed with a linear regression model after log transformation.

Statistical analysis was done in Stata (StataCorp. 2015. Stata Statistical Software: Release 16. College Station, TX: StataCorp LP) and SPSS (IBM Corp., IBM SPSS Statistics for Windows, Version 25.0.0.1, Armonk, New York).

Results

We identified 106 patients with *IDH* mutated, grade 2 diffuse glioma that were treated between 1–1-2007 and 31–12-2018 (Table 1). Mean age at diagnosis was 42.1 years (95 % CI 42.1 – 46.5). Resection status was biopsy only in 17 patients (16%) and a (partial) resection in 89 patients (84%). A 1p/19q codeletion was present in 46 patients (43%), absent in 53 patients (50%), and unknown in 7 patients (7%). 104 patients (98%) were treated to a dose of 50.4 Gy in 28 fractions, 2 patients were treated to a dose of 54 Gy in 30 fractions. Adjuvant chemotherapy was given in 52 patients (49%). A total of 860 MRI's of 106 patients were reviewed. Median number of MRI's per patient was 7 (range 1 – 25). PD occurred in 49 of 106 patients (46%). psPD was identified in 24 of 106 patients (23%) on 76 MRI's (supplementary data). See Fig. 1 for two examples of psPD. In patients with psPD, median number of MRI's with psPD per patient was 2 (range 1 – 11). In this group, 19 of 24 patients were observed to have transient psPD

Table 1
Patient characteristics.

Age (years)	42.1	(95 % 42.1–46.5)	
Sex	Male	68	64%
	Female	38	36%
Hemisphere	Right	43	41%
	Left	56	53%
	Bilateral	4	4%
	Infratentorial	3	3%
Lobe	Frontal	69	65%
	Temporal	15	14%
	Parietal	11	10%
	Occipital	4	4%
	Cerebellum	1	1%
	Brainstem	2	2%
	Overlapping lesion	4	4%
Resection status	Biopsy	17	16%
	Resection, any grade	89	84%
1p/19q codeletion	Non-codeleted	53	50%
	Codeleted	46	43%
	Undetermined	7	7%
Adjuvant chemotherapy	none	54	51%
	PCV	30	28%
	Temozolomide	21	20%
	Other*	1	1%
Radiotherapy dose	50.4 Gy in 28 fractions	104	98%
	54.0 Gy in 30 fractions	2	2%

* One patient started PCV but crossed over to temozolomide.

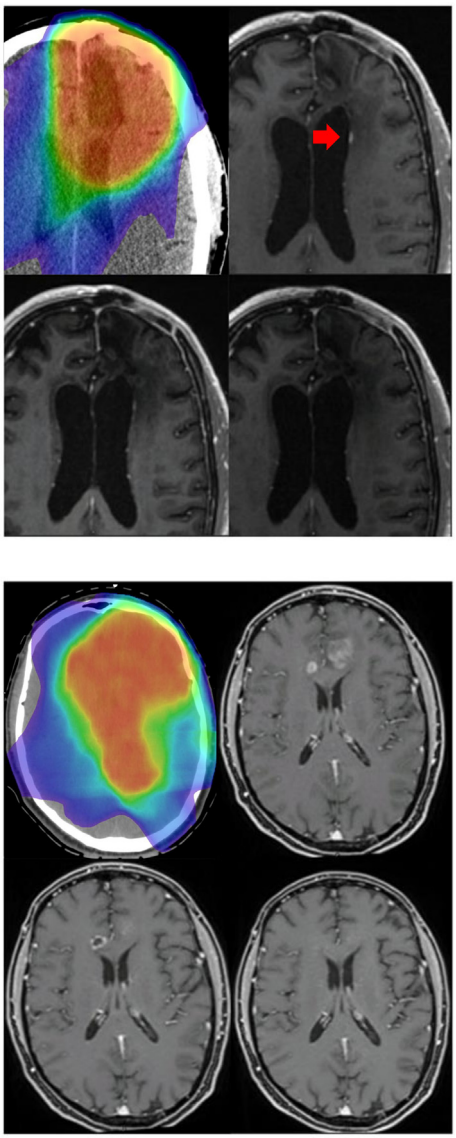

Fig. 1. Two examples of pseudoprogression. Right: Early, transient enhancement of a large oligodendroglioma 3, 6 and 9 months after treatment. Left: small nodular enhancement in the ventricular wall 15 months, 21 months and 27 months after treatment.

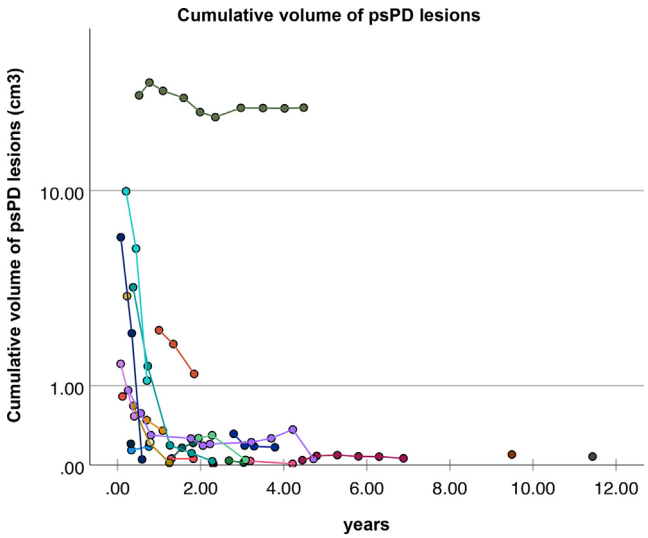

Fig. 2. Cumulative volume of all psPD lesions for individual patients. Timepoints are calculated in years from end of radiotherapy. Note the logarithmic Y-axis. Late onset lesions tend to be smaller.

Table 2
Survival analysis. Presented are Cox-regression parameters that examine the relationship between clinical covariates and the duration of overall survival, progression-free survival, and pseudoprogression-free survival, respectively. Additionally, a Fine and Gray analysis is presented, examining the relationship between clinical covariates and the likelihood of psPD as a failure within the psPD survival curve.

		HR	*P* value
Overall survival median = 8.9 y 95% CI 5.7 – 10.5	1p/19q codeletion: present	**0.39**	**0.02**
	Chemotherapy: any	0.74	0.44
	Resection status: biopsy	1.1	0.82
Progression-free survival median = 4.6 y 95% CI 4.0 – 7.0	1p/19q codeletion: present	0.62	0.16
	Chemotherapy: any	**0.39**	**0.01**
	Resection status: biopsy	1.54	0.2
psPD - free survival median = 3.3 y 95% CI 2.9 – 4.4	1p/19q codeletion: present	0.91	0.07
	Chemotherapy: any	0.62	0.06
	Resection status: biopsy	**1.87**	**0.04**
		SHR	***P*** value
Fine and Gray psPD from psPDfs	1p/19q codeletion: present	**2.34**	**0.05**
	Chemotherapy: any	1.15	0.73
	Resection status: biopsy	1.85	0.19

(79%) and in 5 of 24 patients (21%) psPD remained stable until end of follow-up for at least 12 months. In the group of transient psPD, median duration of psPD was 0.9 years (0.4 – 5.0). psPD was classified as asymptomatic in 69 of 76 MRI's that showed psPD (91%). All instances of symptomatic psPD occurred in 4 of 24 patients with psPD (17%). A total of 95 lesions were delineated, with 82 of 95 lesions (86%) situated within the original GTV and 19 of 95 lesions (20%) within the ventricular fringe. The mean of the maximal lesion volume for all patients was 2.4 cc (95% CI 0.12 – 4.9). Lesion volume decreased with time after radiotherapy (p = 0.03, see Fig. 2). Minimal dose to psPD lesions was 50.1 Gy (95% CI 48.0 – 52.3) and maximal dose was 52.0 Gy (51.6 – 52.3). At the time of analysis, the median length of follow-up in patients still alive was 4.4 years (range 0.3 – 13.2). A total of 38 of 106 patients had died (36%) and the projected OS was 8.9 years (95% CI 5.7 – 10.5) (Table 2). On univariate Cox analysis, there was a significant effect of 1p/19q codeletion (HR 0.39, $p = 0.02$) on OS. There was no significant effect of chemotherapy (HR 0.74, $p = 0.44$) or resection status (HR 1.1, $p = 0.82$) on OS. PD occurred in 49 of 106 patients (46%) and median PFS was 4.6 years (95% CI 4.0 – 7.0). On univariate Cox analysis, there was a significant effect of chemotherapy (HR 0.39, $p < 0.01$) on PFS. There was no significant effect of 1p/19q codeletion, (HR 0.65, $p = 0.16$) or resection status (HR 1.54, $p = 0.2$) on PFS. Median psPDFS was 3.3 years (95% CI 2.9 – 4.4). The cumulative incidence of psPD was 13% at 1 year, 22% at 5 years, and 28% at 10 years (Fig. 3). Median interval between end of radiotherapy and psPD was 0.9 years (range 0.3 – 7.6). On univariate Cox analysis, there was a significant effect of resection status (HR 1.87, $p = 0.04$) on psPDFS. There was no significant effect of chemotherapy (HR 0.62, $p = 0.06$), and 1p/19q codeletion (HR 0.91, $p = 0.07$) on psPDFS. Comparing the subhazard distribution for the failure psPD in a Fine and Gray analysis, a significant effect

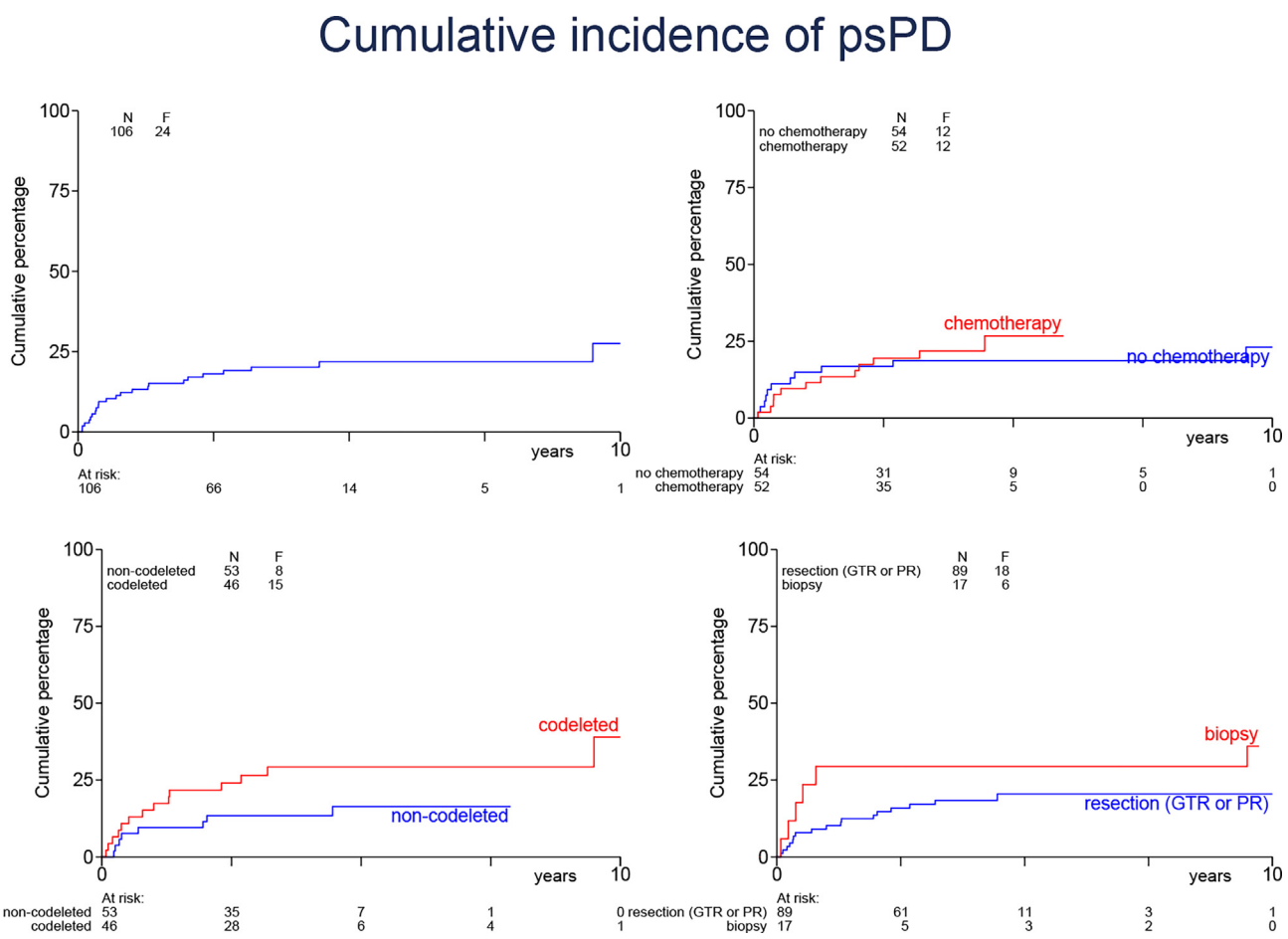

Fig. 3. Incidence of psPD from psPD free survival, with death from any cause and PD as competing risks. N = number of cases, F = number of events. Individual curves are shown for 1p/19q codeletion (SHR 2.34, p = 0.048, chemotherapy (SHR 1.15, p = 0.73) and resection status (SHR 1.85, p = 0.19).

for 1p/19q codeletion (SHR 2.34, p = 0.05) was found. The effects of chemotherapy (SHR 1.15, p = 0.73) and resection status (SHR 1.85, p = 0.19) did not reach significance. When analyzing psPD as a time-dependent covariate, no difference in OS between the group of patients with and without psPD was found (HR 0.71, p = 0.45) (supplementary data). Of the 24 patients with psPD, 18 (75%) were alive at the end of follow up and 6 (25%) had died of disease. Median OS from onset of psPD was not reached. Nine out of the 24 patients with psPD (38%) had PD after psPD, 15 patients (63%) had no disease progression. Median PFS from onset of psPD was 4.0 years.

Discussion

In this group of WHO grade 2 diffuse glioma patients, defined according to the 2016 WHO criteria, psPD occurred in 24 of 106 patients (23%), with an cumulative incidence of 13% at one year increasing to 28% at 10 years. Most lesions (79%) were observed to disappear completely in patients classified as psPD. The favorable PFS and OS calculated from onset of psPD indicate that psPD is probably not a herald of early PD. An 1p/19q codeletion was found to be associated with a more favorable OS and PFS. The use of chemotherapy was associated with an improvement in PFS but not OS, probably owing to the relatively short duration of follow-up [20]. Although extent of resection is a well-known predictor of survival, there was no effect of resection status in our study, probably due to the small number of patients in the biopsy-only group [21]. The observation that psPD is associated with a more favorable prognosis could not be replicated when psPD is treated as a time-dependent covariate [4,5,8].

Comparing the cumulative incidence of psPD in this series with results from literature is difficult, owing to significant heterogeneity in event definition and statistical analysis between studies (Table 3). Still, some observations can be made. The prevalence of psPD in this cohort of 23% is comparable to the 17% to 35% reported for grade 2 diffuse glioma. Additionally, the median time from end of radiotherapy to onset of psPD of 8.8 months is within the 7.6 months to 14 months previously reported [8,10]. Currently, the published series do not allow for a meaningful comparison of psPD in PT vs XRT.

The minimal dose delivered to the psPD regions was within 95% of the prescribed dose in all cases. The ventricular predilection predicted by the model by Bahn et al [16] was not directly apparent in our dataset, with 20% of lesions occurring within the ventricular fringe. While the relative biological effect (RBE) of photons is constant throughout the dose distribution, in PT the RBE increases at the distal edge of the Bragg peak. This effect can result in an inhomogeneous RBE throughout PT dose distributions used for treating glioma, often in medial structures such as the periventricular zone. As such, it is possible that the periventricular zone is more at risk for psPD in PT than in XRT. Again, making a direct comparison is difficult, as lesions inside the original GTV were excluded from the Bahn model, and 86.3% of all lesions in this dataset are situated within the GTV.

In most patients, psPD seemed to occur without associated symptoms, which may be helpful in clinical decision making on new contrast enhancing lesions encountered during follow up.

Table 3
Overview of series reporting prevalence of pseudoprogression after radiotherapy in adult glioma (WHO 1 – 3). When possible, the prevalence of psPD in the WHO 2 subgroup is calculated from published data.

	Patients (total)	psPD prevalence (total)	Follow up (years)	% PT treatments	Patients (WHO grade 2)	psPD prevalence (grade 2)
Lin, 2016[3]	143	20.0%	n/a	0%	59	17%
van West, 2017[4]	63	20.6%	5.0	0%	63	21%
Bronk, 2018[5]	99	14.1%	3.1	34%	36	*
Acharya, 2018[6]	160	11.3%	2.4	23%	67	n/a
Ahmad, 2019[7]	319	12.9%	6.0	2%	121	**
Dworkin, 2019[8]	119	43.6%	4.8	100%	81	35%
Ritterbush, 2021[9]†	100	14.0%	n/a	57%	33	18%
Eichkorn, 2022[10]	185	25.4%	3.8	100%	160	24%
This study	**106**	**22.6%**	**4.4**	**0%**	**106**	**23%**

* No significant difference in psPD prevalence between grade 2 and 3 was reported.
** 90% of WHO grade 2 cases were in the low dose (<54 Gy) group. The prevalence of psPD in this group was 8%.
† All cases with psPD were in the PT group. No psPD was seen in the photon group.

Additionally, the decision process can be aided by comparing the incidence between psPD and PD within the psPD free survival curve. For example, in the first year, the cumulative incidence of psPD was twofold that of PD (13% vs 6%), while by year three psPD was less likely than PD (19% vs 21%). Several clinical covariates were found to be associated with the occurence of psPD. Similar to previous reports, there is a strong association with the 1p/19q codeletion [5,6]. It is hypothesized that the relatively leaky vasculature and propensity to contrast enhancement seen in oligodendrogliomas is related to this increased incidence of psPD [22]. Although the association between the use of chemotherapy and psPD is well described in high grade glioma, this effect was not seen in this group of grade 2 diffuse glioma. A higher propensity of residual tumor volume to exhibit new contrast enhancement early after radiotherapy might explain the shorter psPD free survival in the biopsy-only group. However, as this group was quite small and risk of psPD was not proportional over time in both groups, a difference in the subhazard radio could not be demonstrated.

Advanced imaging modalities may help in distinguishing psPD from PD. Diffusion weighted imaging, perfusion imaging, FDG and amino acid PET have all been shown to be of additional diagnostic value in high grade glioma [23]. In lower grade glioma, psPD lesions typically are smaller than in high grade glioma, which places additional demands on spatial resolution. Recently, O (2 [18F] fluoroethyl)-L tyrosine PET (FET-PET) has been demonstrated to be of considerable value in differentiating PD from psPD [24,25], although this may be lower in in *IDH* mutated glioma [26]. An interesting alternative to using a single imaging modality is the computerized interpretation of multimodal imaging, which has been shown to outperform individual imaging modalities in distinguishing PD from psPD [27].

Research into radiological outcomes in diffuse glioma would greatly benefit from a shared radiological, radiotherapeutic and neuro-oncological consensus regarding both definition and statistical analysis of psPD. To further this discussion, we described psPD in a well-defined cohort that includes molecular testing, using a sequential definition of endpoints and a method of analysis that accounts for competing risks. There are still some limitations to this study, such as the underrepresentation of adjuvant chemotherapy in this historical cohort. Due to the low number of events it was not feasible to implement a multistate model [28]. Such an approach, as well as extending the duration of follow-up, could be helpful in future comparisons of psPD occurrence between XRT and PT cohorts.

Declaration of Competing Interest

This study was partly funded by a research grant of Varian, a Siemens Healthineers Company. The Erasmus MC Cancer Institute also has research collaborations with Elekta AB, Stockholm, Sweden, and Accuray Inc, Sunnyvale, USA.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2023.109674.

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