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Partial resection offers an overall survival benefit over biopsy in MGMT-unmethylated IDH-wildtype glioblastoma patients

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ABSTRACT

Background

Isocitrate dehydrogenase (IDH)-wildtype glioblastoma patients with *O*^{6}*-methylguanine-DNA-methyltransferase* (MGMT)-unmethylated tumors have the worst outcome of all glioblastoma patients. The overall survival (OS) benefit of partial resection of glioblastoma compared to biopsy only remains controversial specifically in relation to molecular factors. In this report, we analyzed the effect of incomplete resection on OS compared to biopsy only in a cohort of IDH-wildtype glioblastoma patients who were uniformly treated with temozolomide-based chemoradiotherapy (TMZ-CR) after surgery.

Material & Methods

A retrospective study was conducted including only glioblastoma patients who were treated with TMZ-CR after surgery from two centers. Surgical groups were defined as biopsy only, partial resection (PR) or gross total resection depending on the presence of contrast-enhancing tumor on postoperative imaging. IDH-mutation was determined using next generation sequencing technique and MGMT-methylation was analyzed with semi-quantitative methylation-specific polymerase chain reaction. Next to descriptive statistics, univariate and multivariate survival analyses were performed using Kaplan-Meier estimates and Cox regression models.

Results

In total, 159 patients were included. 37 patients underwent biopsy only and 73 partial resections. 99 patients (62.3%) harbored unmethylated tumors. Median OS for the whole patient group was 13.4 months. In the subgroup of patients with unmethylated tumors, PR yielded a median OS of 12.2 months vs 7.6 months for biopsy patients ($P = 0.003$). PR proved an independent beneficial prognostic factor in multivariate Cox regression model, together with age, Karnofsky Performance Score and MGMT-methylation.

Conclusion

In IDH-wildtype glioblastoma patients with MGMT-unmethylated tumors, treated with chemoradiotherapy after surgery, PR yields a significant OS benefit compared to biopsy.

1. Introduction

The contemporary treatment of patients suffering from glioblastoma is based on the so-called "Stupp protocol": temozolomide-based chemoradiotherapy (TMZ-CR) after surgery [1]. Temozolomide is administered both during and after radiotherapy (60 Gy delivered in 30 fractions), if tolerated.

Molecular factors play a key role in the development and prognosis of glioblastoma. Methylation of the *O*^{6}*-methylguanine-DNA-methyltransferase* (MGMT) promoter is one of the most important prognostic factors in glioblastoma patient survival, in part by rendering the tumor tissue more susceptible to the cytotoxic effects of alkylating agents [2,3]. As from the 2016 WHO classification of tumors of the central nervous system, mutation of the *isocitrate dehydrogenase* 1 gene (IDH1) – and, rarely, of the IDH2 gene – is generally accepted as the molecular signature of "secondary glioblastoma" or IDH mutated glioblastoma [4,

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5]. IDH-wildtype and mutated glioblastoma do not only differ in molecular factors, but also in radiological features, patient demographics, clinical course and in prognosis: IDH-wildtype glioblastoma has a significantly worse prognosis than its IDH-mutated counterpart, with a median overall survival (OS) of 15 months compared to 31 months respectively [4,6]. Importantly, 90% of newly diagnosed glioblastoma are IDH-wildtype tumors and in more than half of these cases (about 60%) the MGMT gene promoter will be unmethylated [4,7]. In other words, the majority of newly diagnosed glioblastoma patients will have MGMT-unmethylated IDH-wildtype tumors.

Surgery constitutes a keystone element in glioblastoma treatment [8]. In the past years, several studies sought to demonstrate a resection threshold that would correlate with glioblastoma patient survival [9–13]. A meta-analysis of the relevant literature concluded in 2016 that gross total resection (GTR) offers a significant survival benefit over partial resection (PR) but the quality of the evidence according to the GRADE criteria was moderate to low [14]. In most neuro-oncological centers, the current consensus and practice is that of "maximum safe resection" for glioblastoma patients. However, the literature remains conflicting when it comes to the role of PR. Some reports show a survival advantage associated with PR while others see no benefit in PR over biopsy only [11,15,16]. So, the question remains if incomplete resection offers a survival benefit over biopsy for glioblastoma patients with unfavorable molecular markers who will be treated according to the Stupp protocol. Since surgical resection via craniotomy has higher complication rates than needle biopsy, the answer may play a pivotal role in glioblastoma patient counseling [17].

In this retrospective study, we evaluate the effect of partial resection on OS as compared to biopsy only in a cohort of IDH-wildtype glioblastoma patients who were uniformly treated with radiotherapy and temozolomide after surgery.

2. Material & methods

All glioblastoma patients treated in two Flemish hospitals between 2003 and 2014 were evaluated. In this retrospective study, only adult patients with IDH-wildtype supratentorial glioblastoma and who completed temozolomide-based chemoradiotherapy after surgery were enrolled. 3D-conformal beam or intensity modulated radiotherapy was applied, consisting of 30 fractions of 2 Gy. If tolerated, temozolomide was continued in the adjuvant setting for six cycles. Patients with a known malignant progression from low-grade glioma or with a previous history of any other brain tumor were excluded. Demographic parameters were retrieved from the patient files. OS was measured from the date of surgery to the date of decease. The Belgian Cancer Registry confirmed the date of death. Patients who were alive at the date of database closure (December 31, 2014) were censored for OS. The last date of follow-up collection was September 2017.

At the time of surgery, tumor tissue was stored in the tumor tissue archive. The neuropathologist selected and reviewed a representative formalin-fixed paraffin-embedded tissue block for each case. The pathological diagnosis of glioblastoma was reconfirmed according to the 2016 World Health Organization Classification. Semi-quantitative methylation-specific polymerase chain reaction (qMSP) was used to determine if the MGMT-promoter was methylated, as previously described [18]. Presence of the IDH1/2-mutation was tested using next-generation sequencing (NGS) techniques.

Preoperative as well as postoperative imaging was performed using 1,5 or 3T magnetic resonance imaging systems (Siemens, Erlangen, Germany). Postoperative imaging was performed within 72 h after surgery. Pre- and postcontrast T1 images were compared in order to be able to distinguish in the postoperative setting between blood products and residual contrast-enhancing tumor (RTV). Surgery was categorized into biopsy, PR or GTR. If postoperative imaging showed contrast-enhancement of the size of one voxel or more then surgery was classified as PR, as described by Stummer et al. [19]. Contrary, GTR was accepted when no residual contrast-enhancement was visible. If the 3D-T1 magnetization-prepared rapid acquisition gradient echo (MPRAGE) images (slice thickness of 0.9 mm) could be recovered, tumor volumes were measured using standard neuronavigation software (S7, Medtronic, Louisville, CO, USA) with the semi-automated segmentation technique [20].

Descriptive statistics are reported. Categorical variables were compared using the Pearson Chi square test. If the difference between surgical groups proved significant, pairwise comparisons were made using the Bonferroni correction. The Kruskal-Wallis test was applied for comparing numerical variables between surgical groups. Median OS estimates were calculated using the Kaplan-Meier method and compared with the log-rank test. Univariate Cox regression survival analysis was performed using the following prognostic factors: sex; age; Karnofsky Performance Score (KPS); MGMT-methylation status; surgical resection. Interaction variables were created for extent of resection and methylated MGMT and tested in univariate Cox regression. Next, a multivariate Cox regression model was fitted using prognosticators that proved statistically significant in univariate analysis. Graphical methods were used to assess that the proportional hazards assumption was respected. In Cox regression models, numerical variables were not categorized. P-values $<$ 0.05 using two-tailed test was defined as a statistically significant result. Data processing and statistical analyses were performed using SPSS (IBM SPSS, v26.0, Armonk, NY, USA).

The study was approved by the Ethics Committee of both hospitals (Belgian Registration number B670201730765; UZG 2016/1594; AZD 17004). Due to the retrospective study design and the fact that most patients had passed away at the time of database closure, the need for written informed consent was waived by both committees.

3. Results

In total, 159 patients were included in the study, and divided in three subgroups according to the type of surgery: biopsy only (37 patients), PR (73 patients) and GTR (49 patients). There were no missing data, except for preoperative tumor volume (Table 1). This was missing in 17% of patients because MPRAGE images could not be retrieved, mostly in patients from the 2003–2008 period. Only complete cases were used in analyses of preoperative tumor volume. Although the PR group had the highest median preoperative tumor volume, the differences in preoperative tumor volume between surgical groups were not statistically significant ($P = 0.131$). There were significantly more patients with favorable KPS in the GTR group as compared to the biopsy group (Table 1).

Median OS was 13.4 months for the entire patient cohort. Eight patients were censored for OS. Biopsy patients had a median OS of 8.3 months; PR patients of 13.7 months and GTR patients of 15.6 months (Table 2; Fig. 1). Patients with MGMT-methylated glioblastoma had a median OS of 19.7 months as compared to 11.8 months for patients with unmethylated glioblastoma (log-rank $P < 0.001$). In univariate Cox regression survival analysis, age, KPS, GTR, MGMT-methylation and the interaction variable for GTR and methylated MGMT were significantly associated with OS while sex, preoperative tumor volume, PR and the remaining interaction variables were not (Table 3). Within the group of unmethylated glioblastoma patients, partial resection yielded a significant OS advantage of 4.6 months but there was no significant OS difference between the PR and GTR patients (Table 2). Within the subgroup of methylated tumor patients, a significant OS difference was found between PR and GTR patients but not between biopsy and PR patients (Table 2; Fig. 1). A multivariate Cox regression model was fitted using type of resection, age, KPS and MGMT-methylation status as covariates. PR proved an independent beneficial prognostic factor compared to biopsy (HR = 0.53, $P = 0.003$). Methylation of the MGMT promoter was independently associated with a prominent reduction in hazard ratio (HR = 0.31, $P < 0.001$; Table 4).

Table 1
Synoptic overview of the characteristics, MGMT promoter methylation status and radiological findings of the entire cohort of IDH-wildtype glioblastoma patients and of the subgroups according to surgical classification.

Parameter	All patients (n = 159)	Biopsy (n = 37)	Partial Resection (n = 73)	Gross Total Resection (n = 49)	*P*-value
Sex, *n* (%)					0.627[a]
Female	59 (37.1)	13 (35.1)	25 (34.2)	21 (42.9)	
Male	100 (62.9)	24 (64.9)	48 (65.8)	28 (57.1)	
Age at diagnosis (years)					0.430[b]
Mean	61.5	60.7	61.1	62.5	
Minimum - Maximum	31–80	38–77	40–79	31–80	
Karnofsky Performance Score, *n* (%)					**0.010**[c]
≥70	111 (69.8)	19 (51.4)	52 (71.2)	40 (81.6)	
<70	48 (30.2)	18 (48.6)	21 (28.8)	9 (18.4)	
MGMT gene promoter, *n* (%)					0.912[a]
Unmethylated	99 (62.3)	24 (64.9)	44 (60.3)	31 (63.3)	
Methylated	60 (37.7)	13 (35.1)	29 (39.7)	18 (36.7)	
Preoperative tumor volume					0.131[b]
n (%)	132 (83)	31 (79.5)	61 (83.6)	40 (81.6)	
Median (mL)	26.4	21.5	32.4	22.9	
Minimum – Maximum (mL)	1.6–115.0	1.6–115.0	2.6–106.4	4.6–88.2	
Side, *n* (%)					**0.034**[d]
Left	84 (52.8)	13 (35.1)	45 (61.6)	26 (53.1)	
Right	69 (43.4)	21 (56.8)	25 (34.2)	23 (46.9)	
Bilateral	6 (3.6)	3 (8.1)	3 (4.1)	0 (0)	

[a] Chi square test.
[b] Kruskal-Wallis test.
[c] Chi square test between groups: biopsy - PR, $P = 0.057$; PR - GTR, $P = 0.207$; biopsy - GTR, $P = 0.004$; Bonferroni corrected $P < 0.017$.
[d] Chi square test between groups: biopsy - PR, $P = 0.036$; PR - GTR, $P = 0.166$; biopsy - GTR, $P = 0.048$; Bonferroni corrected $P < 0.017$.

Table 2
Comparison of Kaplan-Meier estimates of median overall survival of surgical groups in the whole patient cohort ($n = 159$) and according to MGMT-methylation status. 95% confidence intervals between brackets.

A. Comparison of the biopsy group with the partial resection group			
	Median overall survival (months)		
	Biopsy	Partial resection	Log-rank *P*
All patients	8.3 (5.72–10.88)	13.6 (11.71–15.62)	0.095
Methylated subgroup	13.8 (5.04–22.50)	18.8 (16.75–20.85)	0.804
Unmethylated subgroup	7.6 (5.59–9.67)	12.2 (9.49–14.91)	**0.002**
B. Comparison of the partial resection group with the gross total resection group			
	Median overall survival (months)		
	Partial resection	Gross total resection	Log-rank *P*
All patients	13.6 (11.71–15.62)	15.6 (14.20–16.94)	0.071
Methylated subgroup	18.8 (16.75–20.85)	31.0 (15.89–46.12)	**0.017**
Unmethylated subgroup	12.2 (9.49–14.91)	13.8 (10.9–16.78)	0.704

4. Discussion

Neurosurgical intervention is almost always necessary in glioblastoma management. After acquirement of tumor tissue, histopathological diagnosis can be established together with the study of molecular markers. Neurological symptoms due to mass effect can be relieved by

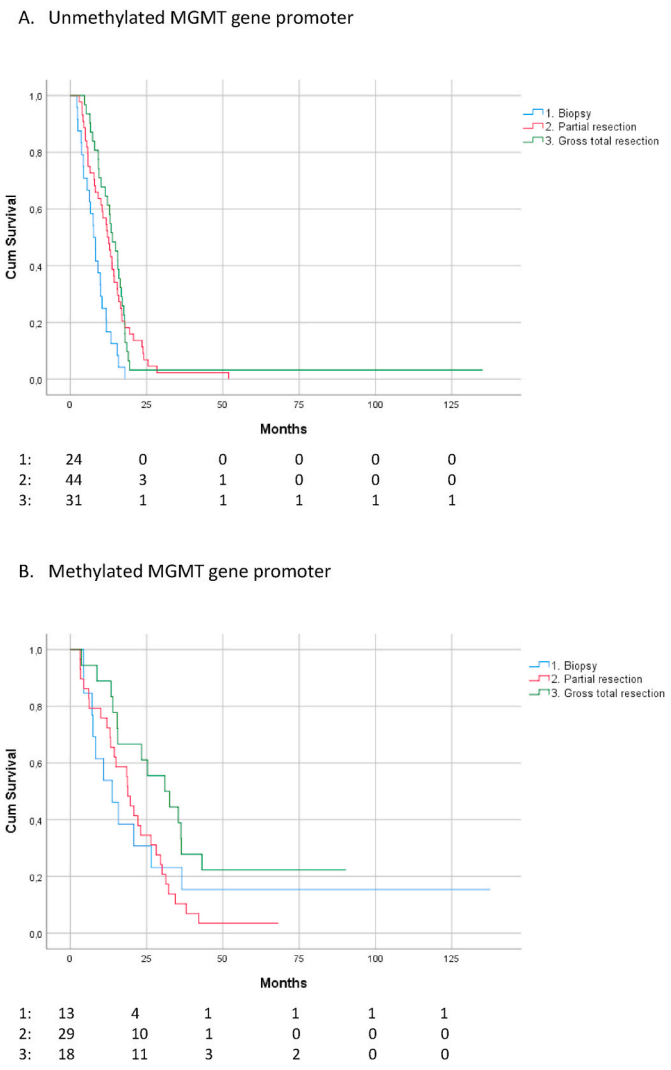

Fig. 1. Kaplan-Meier curves, with numbers at risk, for overall survival of IDH-wildtype glioblastoma patients according to extent of resection.
A Unmethylated MGMT gene promoter
B.Methylated MGMT gene promoter.

Table 3
Univariate Cox regression analysis of overall survival of IDH-wildtype glioblastoma patients. 95% confidence intervals between brackets.

Parameter	Hazard ratio	Wald test *P*
Age[a]	1.03 (1.01–1.04)	**0.002**
KPS[b]	0.98 (0.97–0.99)	**0.005**
MGMT-methylated	0.37 (0.26–0.53)	**< 0.001**
PR (vs biopsy)	0.70 (0.46–1.05)	0.081
GTR (vs biopsy)	0.50 (0.32–0.79)	**0.003**
Sex (male)	0.88 (0.63–1.23)	0.880
Preoperative Tumor volume[c]	1.0 (0.99-1.01)	0.724
I_M*B[d]	0.72 (0.39–1.32)	0.286
I_M*PR[e]	0.70 (0.46–1.06)	0.091
I_M*GTR[f]	0.35 (0.20–0.61)	**< 0.001**

KPS = Karnofsky Performance Score; MGMT = 0^6-methylguanine-DNA-methyltransferase; PR = partial resection; GTR = gross total resection.
[a] Per increment of one year.
[b] Per increment of 10.
[c] Per increment of 1 mL; data available in 83% of patients.
[d] Interaction variable for biopsy and methylated MGMT.
[e] Interaction variable for partial resection and methylated MGMT.
[f] Interaction variable for gross total resection and methylated MGMT.

Table 4
Multivariate Cox regression overall survival model of IDH-wildtype glioblastoma patients ($n = 159$). 95% confidence intervals between brackets.

Parameter	Hazard ratio	Wald test *P*
Age[a]	1.04 (1.02–1.06)	**< 0.001**
KPS[b]	0.98 (0.97–0.99)	**0.025**
MGMT-methylated	0.31 (0.22–0.46)	**< 0.001**
PR (vs biopsy)	0.53 (0.35–0.80)	**0.003**
GTR (vs biopsy)	0.39 (0.25–0.61)	**< 0.001**

KPS = Karnofsky Performance Score; MGMT = 06-methylguanine-DNA-methyltransferase; PR = partial resection; GTR = gross total resection.
[a] Per increment of one year.
[b] Per increment of 10.

tumor resection and steroid dependence may also be reduced. Although the highly infiltrative nature of glioblastoma excludes this tumor as a surgically curable disease, surgery has an important role in oncological control [14]. Recent studies confirmed GTR as an independent prognostic factor for glioblastoma patient survival, and still when molecular factors are considered [21–23]. Concerning PR and survival, however, the evidence is conflicting [11,15,16]. The results from this study show that PR in case of IDH-wildtype glioblastoma results in a significant OS benefit compared to biopsy only patients, specifically in the group of patients with MGMT-unmethylated tumors. Multivariate survival analysis showed that PR is an independent prognosticator, together with age, KPS and methylation of the MGMT gene promoter (Table 4).

Most of the patients with newly diagnosed glioblastoma will have IDH-wildtype tumors with unmethylated MGMT [2,5,7,8]. Obtaining GTR remains a major challenge for neurosurgeons and prospective studies show that GTR may be attainable in only 40% of glioblastoma patients [11,24]. A few years ago, a prospective study found no survival benefit for glioblastoma patients who underwent incomplete resection when compared to biopsy only [11]. Importantly, this study did not take the IDH mutation status into account. Based on the demographic characteristics of the study population, including young patients, it is likely that several patients with IDH mutated glioblastoma were included in the analysis. The possible random imbalance of patients with IDH-mutated glioblastoma between surgical groups, constitutes an important confounding factor in the survival analysis conducted in the report by Kreth and colleagues [11]. Our results acknowledge the conclusion of two recent retrospective studies [15,16]. The patient cohorts and study methodology of those reports are similar to the current study. An important difference is that chemoradiotherapy after surgery was not always uniformly applied in the study by Bette et al. [15]. But the beneficial prognostic effect of surgery was shown in subgroup analysis of the patients treated with chemoradiotherapy and was independent from MGMT promoter methylation status. The report by Sales et al. constitutes a survival analysis of 126 patients with unmethylated MGMT glioblastoma [16]. This is a subgroup analysis from the same initial patient cohort studied by Bette et al. Sales and colleagues found a significant correlation between RTV and survival in this group of patients with unfavorable tumor markers [16]. Our results confirm the conclusion from both reports: in the absence of favorable molecular markers, surgical resection constitutes a statistically significant survival benefit compared to biopsy even if GTR is not obtained. Taken together, the current results and those from the aforementioned reports, considering both MGMT-methylation status and IDH-mutation in survival analysis, weaken the conclusion by Kreth et al.

The current OS results and the analyses of the interaction variables for PR and GTR seem to indicate that resection might have a differential effect according to methylation status (Tables 2 and 3; Fig. 1). However, in the whole patient group as well as in the MGMT-methylation status-based subgroups increasing extent of resection was systematically associated with an OS benefit, but statistical significance was not always reached. This may be explained by the overlap of some confidence intervals which, in turn, could be attributed to the relatively small patient groups and subsequentially lower statistical power. So, definitive results on the presence of a differential effect of surgery related to MGMT-methylation status cannot be drawn from this study. Also, other studies did not show such an effect [11,21,22]. The fact that a 4.6 months OS benefit by PR in the subgroup of MGMT-unmethylated glioblastoma patients is statistically significant (Table 2), underlines the importance of resection, even partial, in this patient subgroup.

Extent of resection was dichotomized in this study into PR and GTR according to the methodology by Stummer et al. and as applied in other reports [11,19,22]. This method has the advantage of simplicity and reproducibility but does not allow to identify a threshold of RTV. In some cases, PR will have been a deliberate choice made by the neurosurgeon and the patient, but in others, the finding of a remnant of contrast-enhancing tumor will have been unexpected. Because of the retrospective design of this study, the reasons for PR could not be ascertained with certitude. It is well known that the perception of glioblastoma resectability varies widely between neurosurgeons, even amongst experts [10,25]. The perception of resectability is influenced by several factors: anatomical tumor localization, including proximity to eloquent zones; patient-related clinical issues; but also, surgeon-related factors including the perceived risks and benefits of neurosurgical resection [25]. This is illustrated by a recent study that compared two large Dutch neuro-oncological centers [26]. Despite the fact that both centers treated comparable glioblastoma patient populations and the fact that in both centers state-of-the-art techniques were available, including awake brain mapping, one center performed significantly more often only biopsy. This may likely be attributed to the aforementioned perceived risks and benefits of (partial) neurosurgical resection. In our opinion, the current study and many previous reports show the benefit of (partial) surgical resection of glioblastoma, even in the era of molecular factors [12–16,19,21–23].

Preoperative tumor volume could be measured on MPRAGE images in most patients (Table 1). Using semi-automated segmentation technique, we tried to diminish observer variability [12,20]. In statistical analysis, preoperative tumor volume was kept as a continuous variable rather than dichotomized, in order to avoid loss of statistical power and confounding [27]. Preoperative tumor volume did not correlate with OS, contrary to the results from previous studies [12,15]. Some differences between these studies and the present one should be noted. In the report by Bette et al. not all patients were treated with chemoradiotherapy and preoperative tumor volume was dichotomized [15]. After inclusion of postoperative chemoradiotherapy in multivariate analysis, preoperative tumor volume lost its statistical significance. The study by Grabowski et al. excluded biopsy patients, resulting in a patient cohort with surgical resection patients only, in contrast to the patient cohort studied here which includes also biopsy patients [12]. Moreover, the relationship between patient survival and glioblastoma tumor volumes is more complex and may depend on volume ratios of different segments rather than on the total tumor volume [28].

This study has several shortcomings. First, the retrospective study design may have introduced selection bias. Next, corticosteroid use at diagnosis was not included in the analysis. Also, therapy for tumor progression or recurrence was neither standardized nor included in the analysis. A threshold for RTV could not be established. This study also has important strengths. First, we present a glioblastoma patient cohort uniformly treated with TMZ-CR after surgery. Second, categorization of patients after surgical resection was straightforward which improves the external validity of the study. Third, we were able to determine molecular factors using sensitive and reliable techniques, notably qMSP and NGS [3,18,29].

5. Conclusion

The debate about the impact of neurosurgical tumor resection on glioblastoma patient survival started already in the beginning of the 20th century. While in 1923 Harvey Cushing reported on glioblastoma

that "the general idea prevails that these tumors represent hopeless surgical lesions" [30], nowadays the practice of maximum safe resection is supported by evidence. Our study adds to the evidence by showing that also in the group of glioblastoma patients with unfavorable molecular markers, partial resection does offer a significant overall survival advantage compared to biopsy only.

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CRediT authorship contribution statement

Giorgio Hallaert: Conceptualization, Methodology, Validation, Formal analysis, Data curation, Writing - original draft, Visualization, Funding acquisition. **Harry Pinson:** Validation, Formal analysis, Data curation, Writing - review & editing. **Dimitri Vanhauwaert:** Resources, Writing - review & editing. **Caroline Van den Broecke:** Resources, Writing - review & editing. **Dirk Van Roost:** Conceptualization, Supervision, Project administration. **Tom Boterberg:** Conceptualization, Project administration, Resources, Writing - review & editing, Funding acquisition. **Jean-Pierre Kalala:** Conceptualization, Project administration, Resources, Writing - review & editing.

Declaration of competing interest

The authors declare that there is no conflict of interest. None of the authors has any commercial interest in the techniques or materials described in this study.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.suronc.2020.10.016.

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