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Original Article

Intraoperative radiotherapy for glioblastoma: an international pooled analysis

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ABSTRACT

Purpose: To report the results of the first international pooled analysis of patients with glioblastoma treated with intraoperative radiotherapy (IORT) in addition to standard of care therapy.
Methods: Data from 51 patients treated at five centers in Germany, China and Peru were analyzed. All patients underwent tumor resection followed by a single application of IORT (10–40 Gy, prescribed to the applicator surface) with low-energy X-rays. Thereafter, standard adjuvant radiochemotherapy and maintenance chemotherapy were applied. Factors of interest were overall survival (OS), progression-free survival (PFS), local PFS (L-PFS; defined as appearance of new lesions ≤1 cm to the cavity border) and distant PFS (D-PFS; lesions >1 cm). The same endpoints were estimated at 1-, 2- and 3-years using the Kaplan-Meier method. Additionally, rates and severity (as per Common Terminology Criteria for Adverse Events Version 5.0) of radionecrosis (RN) were analyzed.
Results: The median age was 55 years (range: 16–75) and the median Karnofsky Performance Status was 80 (20–100). At a median follow-up of 18.0 months (2–42.4), the median OS, PFS, L-PFS and D-PFS were 18.0 months (95% CI: 14.7–21.3), 11.4 months (95%CI: 7.58–15.22), 16 months (95%CI: 10.21–21.8) and 30.0 months (95%CI: 18.59 – 41.41), respectively. The estimated 1-, 2- and 3-year OS, PFS, L-PFS and D-PFS were 79.5%, 38.7% and 25.6%; 46.2%, 29.4%, and 5.9%; 60.9, 37.9%, and 12.6%; and 76.7%, 65.0%, and 39.0% respectively. First progression occurred locally in only 35.3% of cases. Grade 1 RN was detected in 7.8% and grade 3 in 17.6% of the patients. No grade 4 toxicity was reported and no treatment-related deaths occurred.
Conclusion: Compared to historical data, this pooled analysis suggests improved efficacy and safety of IORT with low-energy X-rays for newly diagnosed glioblastoma. Prospective data is warranted to confirm these findings.

Glioblastoma (GB) represents the most frequent primary malignancy of the brain in adults, accounting for more than half of all gliomas [1]. Survival times are still narrow and range between 1 and 3 years [2–6]. Even patients with favorable risk factors, such as young age, high Karnofsky performance status (KPS) and hypermethylation of the O^6-methylguanine-DNA-methyltransferase (MGMT) promoter suffer from tumor recurrence, usually occurring 14–17 months after therapy [2,6].

Despite technical advances, including neurophysiology-, neuronavigation- and fluorescence-guided gross total resection (GTR); local tumor re-growth remains the most frequent pattern of failure [7–10]. As tumors start repopulating the cavity immediately after surgery and even during radiotherapy [11,12], we proposed to overcome this spatial and temporal miss using additional low-energy intraoperative radiotherapy (IORT) [13], which is applied immediately after surgery and, due to the unique

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physical characteristics of low-energy photons, restricted to the surgical margin.

Recently a prospective, single-arm phase I/II study was conducted to determine the safety and efficacy of IORT with low-energy X-rays added to standard of care adjuvant therapy (radiochemotherapy and maintenance chemotherapy) [14]. It was shown that the addition of IORT was not only tolerable, but also yielded a median local progression-free survival of roughly 18 months despite a high portion of patients with post-operative residual disease (13 of 15) and unmethylated MGMT promoters (10 of 15) in the trial [15].

The encouraging data from this trial has not only prompted the initiation of a randomized phase III trial (NCT02685605), but also a variety of single-arm mono-institutional studies. We here present an international pooled analysis of patients treated with low-energy IORT at five institutions from three different countries, in addition to standard of care therapy. It resembles the largest cohort of patients that have received this therapy so far.

Methods

Patients from five centers (located in Germany, Peru and China) were retrospectively included in this analysis. All patients were diagnosed with suspected GB/high-grade glioma in pre-treatment magnetic resonance imaging (MRI) and subsequently underwent surgery. Only patients with confirmed pathology diagnosis of GB were included in the analysis. IORT was delivered as described previously after frozen sections supported the preliminary diagnosis of glioblastoma [14,15]. In brief, 50-kV X-rays (INTRABEAM, Carl Zeiss Meditec AG, Oberkochen, Germany) were applied using spherical applicators (size range 1.5–5 cm) at dose levels ranging from 10 to 40 Gy prescribed to the surgical margin (0 cm depth, i.e. the applicator surface). Following surgery, all patients received standard-of-care adjuvant therapy, consisting of 60 Gy intensity-modulated or volumetric-modulated arc (IMRT-VMAT) external-beam radiotherapy (EBRT) and concomitant temozolomide chemotherapy followed by maintenance temozolomide chemotherapy (2). Thereafter, response was assessed at 8–12 week intervals using multiparametric MRI, and updated RANO criteria [16].

Factors of interest were median overall survival (OS), median progression-free survival (PFS), median local PFS (L-PFS, with local recurrence being defined as tumor recurrence within 1 cm to the cavity margin), median distant PFS (D-PFS, with a distant recurrence being defined as any new lesion occurring >1 cm from the cavity margin), and radionecrosis rates (RNR). Multiparametric MRI included Perfusion sequences to account for pseudoprogression, according to clinical criteria and local follow-up protocol. In addition, estimated cumulative rates for these endpoints were calculated for 12, 24 and 36 months using the Kaplan–Meier method. Severity was assessed based on Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All statistical analyses were performed using SPSS (V. 24.0; IBM, Armonk, NY).

Results

Patients characteristics

A total of 51 patients were treated with IORT in addition to standard-of-care. The median age was 55 years (range: 16–75 years) and the median KPS was 80 (20–100). MGMT promoter hypermethylation was absent in 39.2% of patients. IDH1 was found to be wild type in 76.5% and mutated in 9.8% of patients. Satellite lesions were present in 15.7% of the patients. Depending on local practices, site-specific protocols and/or constraints of organs-at-risk (mainly chiasm, optical nerves, brain stem) applied doses ranged from 10 to 40 Gy, with most of the patients receiving 10 Gy. Dose distribution curves are shown in Figs. 1 and 2 for a 3 cm diameter Spherical applicator. Adjuvant EBRT was applied in all but one patient and 44 of 51 patients received temozolomide-based chemotherapy (Table 1).

Treatment outcomes

At a median follow-up of 18 months (range: 2–42.4 months), the median OS was 18.0 months (95% confidence interval [CI]: 14.7–21.3 months; Fig. 3a). The OS rates estimated at 12, 24, and 36 months were 79.5%, 38.7% and 25.6% respectively. The median (overall) PFS was 11.4 months (95%CI: 7.6–15.2; Fig. 3b) and the PFS rates at 12, 24, and 36 months were 46.2%, 29.4%, and 5.9%. The median L-PFS was 16 months (95%CI: 10.2–21.8; Fig. 3c), with annual estimated L-PFS rates of 60.9, 37.9%, and 12.6%. The median D-PFS was 30 months (95%CI: 18.6–41.4, Fig. 3d), with estimated

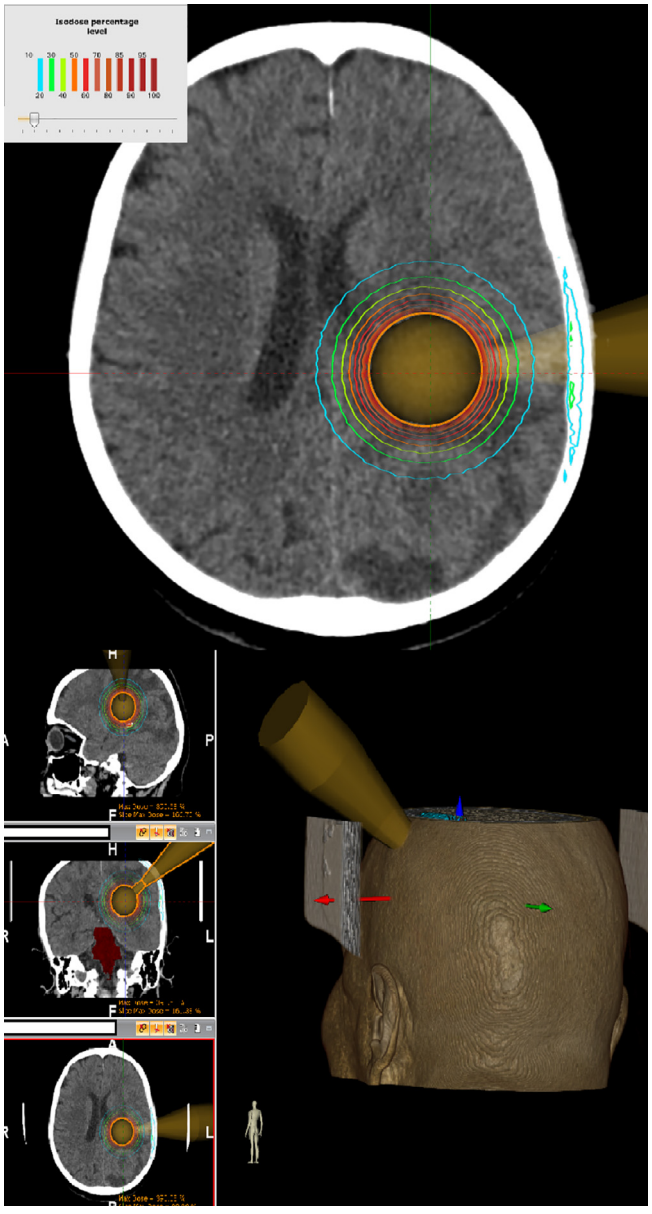

Fig. 1. Isodose distribution in parenchyma for 30 Gy prescribed at applicator's surface. Delivery of ~20% of total prescribed dose after 1 cm, might vary with applicator size.

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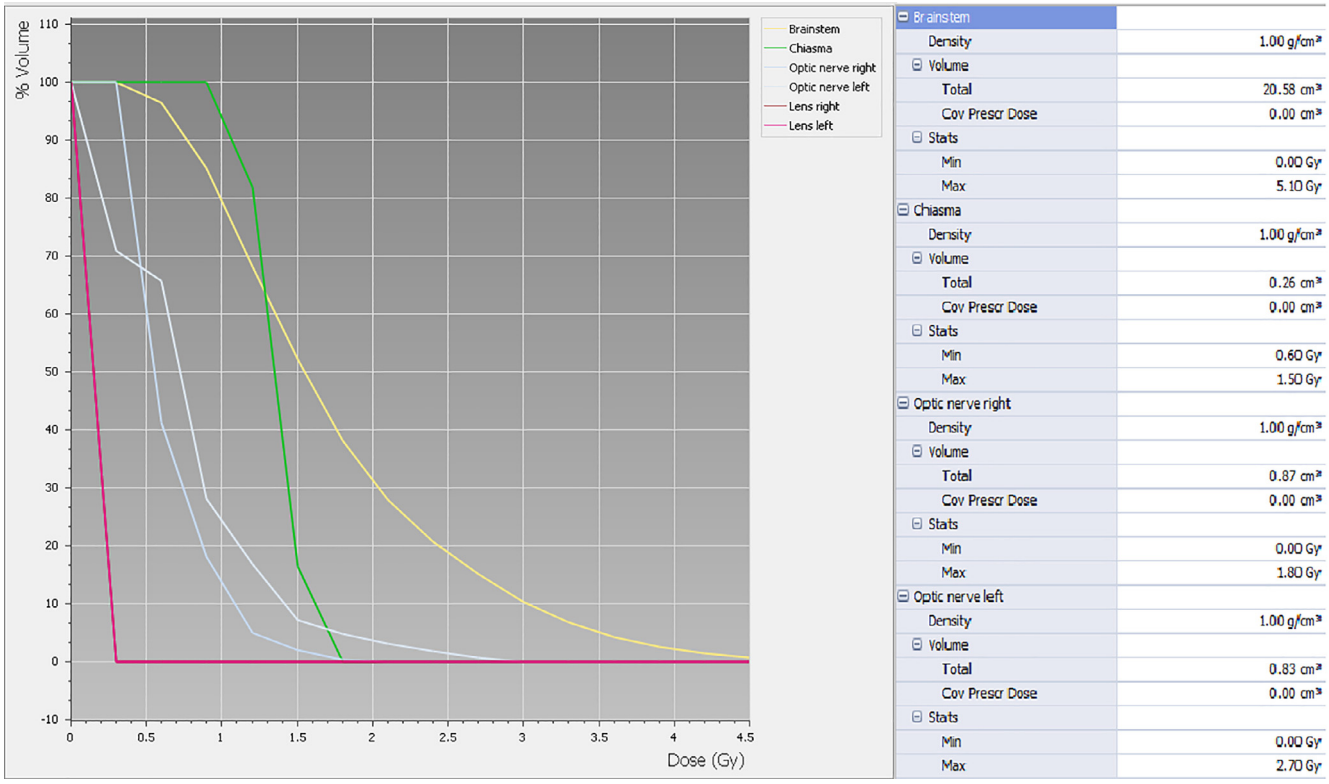

Fig. 2. DVH graphic with organs-at-risk dose.

Table 1
Baseline patient characteristics and treatments. Data are either N or median unless stated otherwise. Legend: MGMT, O6-methylguanine-DNA-methyltransferase; IDH1, Isocitrate dehydrogenase 1; IORT, intraoperative radiotherapy; EBRT, external-beam radiotherapy.

Characteristics	N/Median (Range)	%
Median Age (years)	55 (16–75)	
Median KPS	80 (20–100)	
Gender		
Male	28	54.9
Female	23	45.1
Satellite Lesions[†]		
Present	8	15.7
Absent	42	82.3
Unknown	1	2
MGMT		
Methylated	17	33.3
Unmethylated	20	39.2
Unknown	14	27.5
IDH1 Status		
IDH1 wild type	39	76.5
IDH1 R132H mutation	5	9.8
Unknown	7	13.7
IORT Dose[‡]		
10 Gy	23	45.1
20 Gy	9	17.6
30 Gy	15	29.4
40 Gy	4	7.8
IORT delivery time (min)	17 (5–58)	
Adjuvant EBRT[*]		
Yes	50	98
No	1	2
Chemotherapy[#]		
Yes	44	86.3
No	3	5.9
Unknown	4	7.8

[†] Defined as separate T1-contrast-enhancing lesion within the edema visible in T2.
[‡] Prescribed to the applicator surface.
[*] Total dose 60 Gy, given in 20 fractions.
[#] Includes concomitant (75 mg/kg/d) and maintenance (150–200 mg/m2, 5/28 scheme) temozolomide chemotherapy.

rates of 76.7%, 65.0%, and 39.0% per year. First progression occurred locally in only 35.3% of cases (Table 2).

Toxicity profile

Radionecrosis was judged to be present in 13 patients (25.5%), which is in line with previous findings in a phase I/II trial (15). RN was scored to be of grade 1 RN in 4 patients (7.8%) and of grade 3 in 9 patients (17.6%). There was no significant relation between RN and OS, PFS and L-PFS; however, a difference in D-PFS was found, favoring patients that developed RN against those who did not, as no patient from this group ($n = 9$) developed distant progression and 15 from the non-radionecrosis ($n = 42$) group presented this toxicity ($p = 0.047$). No grade 4 or 5 toxicity related to IORT was found in this cohort and no treatment-related deaths occurred (Table 3).

Discussion

Surgery resembles one of the most important components of glioblastoma therapy and novel technology may allow to identify and resect almost all macroscopically visible tumor [17]. Although it appears sound that there is a direct correlation between the amount of tumor removed and outcome [18], surgery-related neurological deficits may ultimately counteract all benefits [19], which often results in "maximum safe" than "gross total" resections. However, even after (macroscopic) complete resection of glioblastoma, a considerable number of tumor cells will remain in the cavity [20]. These cells are capable to rapidly re-populate the margin as demonstrated in comparative analyses of early post-operative and pre-radiotherapy scans [11,12].

Few improvements of glioblastoma therapy were achieved over the past decades: Patients with favorable (epi)genomic profile [21,22] benefit from the addition of temozolomide (2) and lomus-

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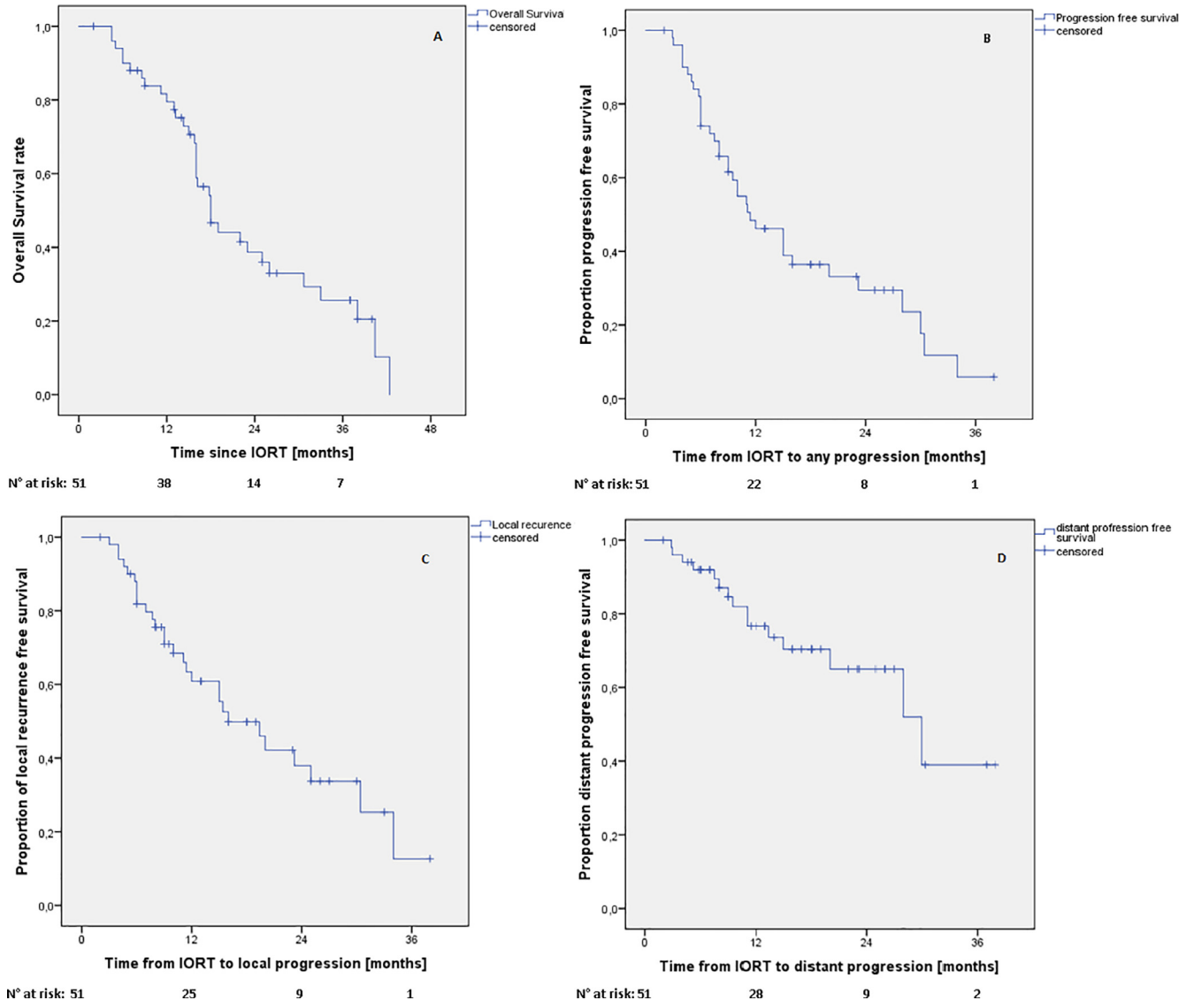

Fig. 3. Kaplan–Meier curves for Overall Survival (a), Progression-free survival (b), Local recurrence-free survival (c), and Distant recurrence-free survival (d).

tine (6) to radiotherapy. Alternating electric fields may delay tumor growth by inhibiting cell division independent of the molecular subtype [23]. The general approach of external-beam radiotherapy (EBRT), however, has not significantly changed since the 1980s, where a regimen of 60 Gy given in 30 fractions of 2 Gy was established [24,25]. Although some technological advances (such as intensity-modulated radiotherapy) increased the conformity of EBRT, dose escalation studies yielded conflicting results in terms of overall survival benefit [26–30].

Intraoperative radiotherapy does not require extra radiation to travel through healthy tissue as compared to EBRT, thus allowing for local dose escalation at the site of most likely recurrence [34–36]. In contrast to intraoperative electron radiotherapy (IOeRT), that may leave several aspects of the cavity uncovered [31,32], a more intuitive approach is to modify the dose distribution and to spherically cover the cavity with low-energy X-rays [33]. In a recent phase I/II trial, this novel approach of local dose escalation yielded a median progression free survival of 11.2 months and a median local progression-free survival of 14.3 months, with isolated distant recurrence as predominant pattern of failure [15].

The pooled analysis here presented confirms these findings in a larger patient collective and suggests superiority compared to historical data as the median PFS in the benchmarking EORTC trial was 6.9 months (2) with no notable improvements in standard-of-care arms in contemporary studies [4,5]. Despite the limitations of our study, the reported OS rate at 3 years (25.6%) reinforces the improved outcomes hypothesis, as the aforementioned seminal trial reported similar outcomes after 2 years follow-up (26.5%).

One of the main concerns about achieving a radical dose at brain tissue is the development of radionecrosis. This side effect has been the limiting burden for dose escalation, although brachytherapy dose-escalation reports suggested less severe complications rates than only EBRT-based approaches, with incidences ranging from 4 to 27%, [26,37]. The rate of radionecrosis in this analysis (25.1%) was seen to be higher than after standard of care (5–10%) [38] but lower than in the INTRAGO trial (33%) or after interstitial brachytherapy (~50%) [39]. However, in the light of a potential correlation between radionecrosis and improved outcome [40] and the availability of a drug (bevacizumab) that highly effective terminates symptomatic radionecrosis [41], we consider this side effect as manageable and thus acceptable given the benefit of the treatment. This results interesting as we found a significant correlation between RN and improvement of D-PFS ($p = 0.047$), suggesting a local immune response boosting;

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Table 2
Clinical outcomes after IORT plus standard of care.

Endpoint	N	%
Progression		
Any progression	36	70.6
First site local	18	35.3
First site distant	18	35.3
No progression	15	29.4
Any local failure		
Yes	28	54.9
No	23	45.1
Distant failure		
Yes	15	29.4
No	36	70.6
Vital signs/cause of death		
Deceased	37	72.5
Tumor progression	21	41.2
Other causes	12	23.5
Not reported	4	7.8
Alive[†]	14	27.5
Salvage Therapy		
Yes[‡]	24	47.1
No	27	52.9

[†] At a median follow up 18 months.
[‡] Salvage therapies included re-surgery (n = 5 patients), re-irradiation (n = 9), other systemic therapies (n = 18)

Table 3
Incidence of radionecrosis (RN).

Radionecrosis	N	%
any RN	13	25.2
Severity[†]		
Grade I	4	7.8
Grade II	0	0
Grade III	9	17.6
Grade IV	0	0
Grade V	0	0

[†] Assessed based on Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

although these results should be taken carefully, as the number of patients included in this subgroup (n = 9) might generate a bias in the outcomes.

In conclusion, compared to historical data, this analysis of the largest cohort of patients so far suggests that IORT with low-energy X-rays added to standard-of-care therapy in glioblastoma improves local control and survival without major side effects. A recently initiated multinational randomized phase III trial is currently testing the impact of IORT added to standard of care versus standard of care alone (ClincalTrials.gov ID NCT02685605).

Disclosures

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X.H.: Nothing to disclose.

G.J.S.: Nothing to disclose.

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S.B.: Nothing to disclose.

B.F.: Nothing to disclose.

S.M.: Nothing to disclose.

H.Z.: Nothing to disclose.

S.Q.: Nothing to disclose.

X.Q.: Nothing to disclose.

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Ethics

Approved by the Ethics Committees of each institution, according to local protocols.

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