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Angaben zur Veröffentlichung / Publication details:

Shiban, Ehab, Philipp Krauss, Tina Schaller, Ina Konietzko, Tatiana Mögele, Nicola Jungbäck, Dorothee Mielke, et al. 2025. "A prospective observational study of inflammatory mediators in cerebrospinal fluid after intraoperative radiotherapy of brain tumors." Therapeutic Advances in Medical Oncology. https://doi.org/10.1177/17588359251389740.

THERAPEUTIC ADVANCES in
Medical Oncology

Original Research

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Ther Adv Med Oncol

2025, Vol. 17: 1–13

DOI: 10.1177/17588359251389740

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Abstract

Background: Malignant brain tumors, including gliomas and brain metastases, present therapeutic challenges due to their aggressive nature and high recurrence rates. Intraoperative radiotherapy (IORT) is a promising novel therapeutic approach that delivers immediate irradiation to the resection cavity. This may trigger a local and systemic immune response. However, the immunological effects of IORT remain poorly understood.

Objectives: To investigate the immunomodulatory effects of IORT by analyzing perioperative profiles of inflammatory mediators (IMs) in patients undergoing surgical resection of malignant brain tumors.

Design: A prospective observational cohort study comparing IM responses in patients undergoing brain tumor resection with and without IORT.

Methods: In total, 44 patients undergoing surgical resection of brain tumors were included, with 20 receiving IORT and 24 serving as controls without IORT. In both groups, cerebrospinal fluid/wound fluid samples were collected from the resection cavity at several predefined intraoperative and postoperative time points. A multiplex proteomic assay was used to measure 19 IM involved in inflammation and immune activation.

Results: IORT significantly increased the levels of seven IM (interleukin (IL)-1β, IL-6, IL-8, IP-10, MCP-1, MIP-1β, and VEGF) within the IORT group compared to baseline levels. When comparing to the non-IORT group, the increase in IL-1β was significantly greater for patients with metastases, while IL-10 also showed a trend toward significance.

Conclusion: IORT induces distinct changes in levels of IM, which may contribute to improved tumor control. These findings provide novel insights into the immunomodulatory effects of IORT and may have implications for optimizing multimodal treatment strategies for malignant brain tumors. As an exploratory study with a limited sample size, the findings should be interpreted as hypothesis-generating.

Keywords: brain tumor microenvironment, cerebrospinal fluid, intraoperative radiotherapy, neuroinflammation

Received: 30 April 2025; revised manuscript accepted: 6 October 2025.

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Introduction

Malignant brain tumors, including primary malignancies such as gliomas, and brain metastases (BM) as secondary brain tumors, present a major clinical challenge due to their aggressiveness, high recurrence rates, and limited treatment options.[1,2]

Surgical resection remains the first-line therapy to reduce tumor mass and provide tissue for diagnostic assessment.[3,4] However, residual tumor cells often persist in surrounding brain tissue, necessitating adjuvant therapies. Radiotherapy (RT), alongside chemotherapy, is a key component of postoperative treatment aimed at improving local tumor control.[5,6]

A significant limitation of standard RT is the delay between surgery and its initiation, which allows residual tumor cells to repopulate.[7] Furthermore, defining accurate target volumes can be complicated by dynamic changes in the postoperative resection cavity,[8,9] while radiation exposure to healthy brain tissue restricts the therapeutic window.[10,11]

Intraoperative radiotherapy (IORT) has emerged as a promising alternative. By delivering a single high-dose irradiation directly to the resection cavity during surgery, IORT offers several advantages: immediate targeting of residual tumor cells, reduced need for adjuvant RT, minimization of damage to healthy brain tissue,[12] and the potential to trigger immune responses with local and systemic effects.[13]

It has been hypothesized that IORT alters the postoperative microenvironment,[14,15] disrupting tumor-promoting signals and modulating local inflammation.[16]

Increasing evidence suggests that radiation-induced immune responses contribute significantly to treatment success, as seen in reduced radiotherapy efficacy in immunosuppressed patients and systemic antitumor effects after localized irradiation.[17] Cytokines such as TNF and interleukins (IL-1, IL-6) are known mediators of these immune responses.[18] These cytokines initiate an immune response directed against the tumor as regulators of the innate and adaptive immune systems.[19]

This study aimed to characterize alterations of inflammatory mediator (IM) in patients with malignant brain tumors following IORT with the hypothesis that IORT induces a distinct local immunological response detectable in early postoperative fluid samples, reflecting both its immunomodulatory potential and interaction with the tumor microenvironment. To do so, analyzed cerebrospinal fluid and resection cavity wound fluid to identify specific IM signatures. Our goal was to explore potential biomarkers of IORT response and gain deeper insight into its immunomodulatory effects and influence on the tumor microenvironment.

Materials and methods

Patients

This prospective observational cohort study included patients (⩾18 years of age) who underwent surgical resection of malignant brain tumors at the University Medical Center Augsburg between February 2023 and December 2024 and provided informed consent. Patients with prior radiotherapy or immunotherapy were excluded. Given the exploratory nature of the study, no formal sample size calculation was performed, and the sample size was determined pragmatically based on the number of eligible patients treated during the study period at our institution.

IORT was applied according to local multidisciplinary tumor board recommendations prior to surgery, based on clinical indication, tumor entity, patient-specific factors (e.g., tumor location and accessibility for IORT, tumor size, and intraoperatively feasibility of IORT), and technical availability of the IORT device at the time of surgery. Thus, group allocation was not randomized but reflected clinical decision-making and logistical feasibility in routine practice.

The study was approved by the ethics committee of LMU Munich (approval no. 22-0554). CSF/wound fluid (hereafter referred to as CSF) from the resection cavity or surgical access route was obtained from patients in the study group (IORT group) and from the control group (non-IORT group).

For the IORT group, four, for the non-IORT group, three time points were defined for CSF sampling:

IORT cohort:

- (T1-IORT) Pre-resection: intraoperatively, before tumor resection.
- (T2-IORT) Post-resection, pre-IORT: intraoperatively, after tumor resection, before IORT.
- (T3-IORT) Post-IORT: intraoperatively, (immediately) after tumor resection and IORT.
- (T4-IORT) Postoperative: ~24 h postoperatively from drainage.

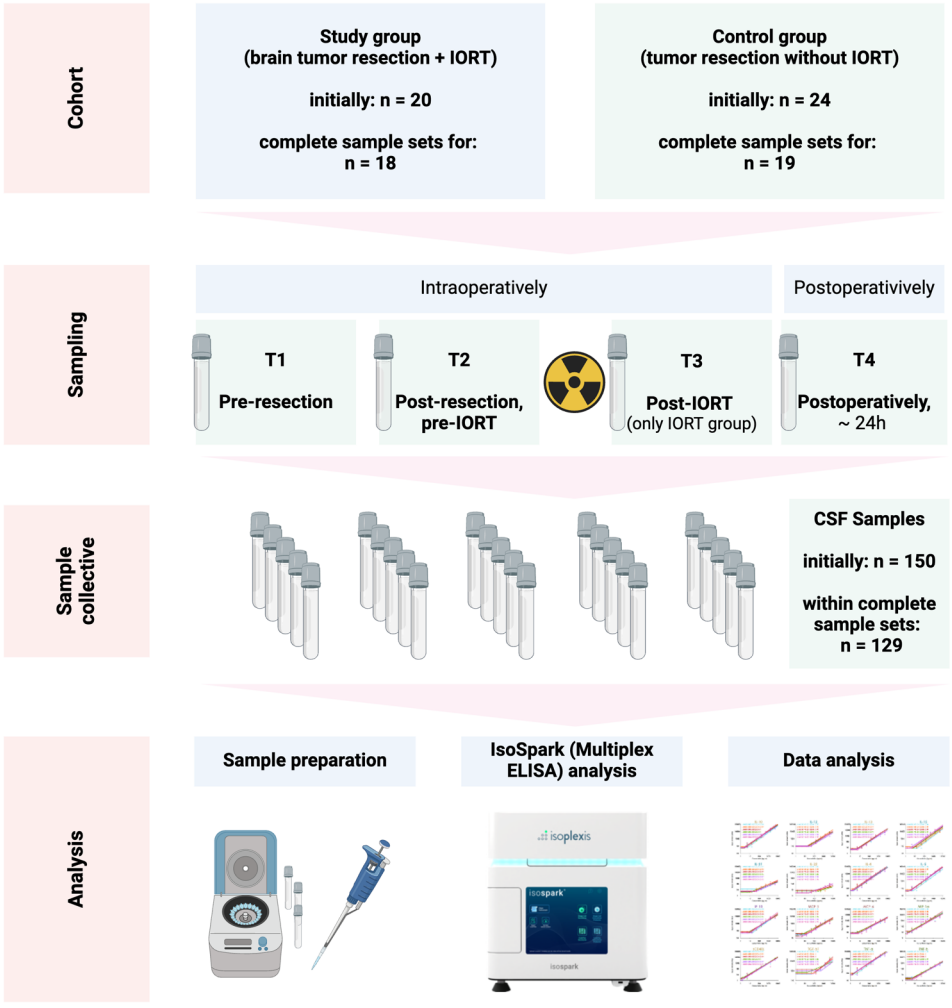

Figure 1. Graphical abstract of the study design.

Non-IORT cohort:

- (T1-nonIORT) Pre-resection: intraoperatively, before tumor resection.
- (T2-nonIORT) Post-resection: intraoperatively, after tumor resection.
- (T4-nonIORT) Postoperative 24 h: ~24 h postoperatively from drainage.

The study design is illustrated in Figure 1. The reporting of this study conforms to the STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology) for cohort studies.[20] A completed STROBE checklist is provided in Supplemental Material S1.

Intraoperative radiotherapy

IORT was administered directly after tumor resection using the INTRABEAM system (Zeiss Meditec AG, Oberkochen, Germany), applying 20 Gy for metastases and 30 Gy for gliomas (50 kV X-rays). Irradiation time was determined individually as reported previously.[21,22] Applicator size was selected according to the size of the resection cavity.

Sample handling

CSF volumes were recorded, centrifuged twice within 2 h to remove cells, aliquoted, and frozen at −20°C. Samples obtained outside working hours were pre-frozen and processed the next

day. Literature supports this approach as suitable for IM analysis.[23,24]

Multiplex analysis of IMs

IM levels were measured using the multiplex immunoassay CodePlex Secretome® solution for IsoSpark® technology (Bruker Cellular Analysis, Emeryville, CA, USA). The macrochambers of the CodePlex® chip were pre-patterned with a 19-plex antibody array. Samples were thawed at room temperature and filled into each well of a chip in replicates (5.5 µl per replicate) as previously described.[25,26] Two percent bovine serum albumin diluted in phosphate-buffered saline was used for background measurements. The chip was then loaded into an IsoSpark® system, and IM levels were measured in the bulk using a fluorescence enzyme-linked immunosorbent assay (ELISA)-based multiplex assay in an automated workflow. Results were quantified by IsoSpeak® software v3.0.1 (Bruker Cellular Analysis) using the Human Innate Immune Panel® (Bruker Cellular Analysis, Emeryville, CA, USA). This predefined panel comprises 19 cytokines, chemokines, and growth factors selected for their established relevance in inflammation and immune activation, and was chosen because early effects after IORT were expected to involve the innate immune system. The following IMs were analyzed: EGF, GM-CSF (CSF2), Granzyme (GZMB), IFN-γ (IFNG), IL-10, IL-15, IL-1β, IL-4, IL-6, IL-7, IL-8 (CXCL8), IP-10 (CXCL10), MCP-1 (CCL2), MIP-1a (CCL3), MIP-1b (CCL4), PDGF-BB, sCD137 (TNFRSF9), TFN-α, and VEGF.

Outputs were averaged between replicates and given in relative fluorescence units.

Quality controls

1. Dilution control: Selected samples were tested undiluted and diluted (1:2) at study start and in November 2024; no inhibition was detected.
2. Reproducibility control: Intra-assay variability was assessed through duplicate/triplicate measurements.

Statistical analysis

Statistical analyses were performed using IsoSpeak® software v3.0.1 (Bruker Cellular Analysis) and R (version 4.3.3; RRID:SCR_001905). Paired comparisons used the Wilcoxon signed-rank test, and group comparisons the Mann–Whitney *U* test. Quantitative variables such as IM levels were treated as continuous variables. Only unadjusted comparisons were performed due to the exploratory nature of the study and limited sample size. Differential IM levels were calculated as the $\log_2$ fold change ($\log_2$FC) relative to baseline (T1) at each subsequent time point. A p-value <0.05 was considered statistically significant.

Results

Patients and tumor characteristics

In total, 44 patients were recruited (20 IORT, 24 non-IORT), yielding 150 CSF samples (mean volume 1.35 ml; range: 0.05–5.00 ml). Of these, 37 patients (18 IORT group, 19 non-IORT) provided complete sample sets across all defined time points and were included in the analysis.

The median patient age was 66 years (range: 26–86). Most IORT patients had metastases ($n = 15$). The non-IORT group consisted of 11 patients with metastases and 8 patients with primary brain tumors (Table 1, Table S2).

Dynamics of IMs between different time points following IORT

The structured sampling design allowed differentiation between surgery-induced and IORT-specific immune responses. The IM levels are given as the $\log_2$FC and $\log_2$FC differences, respectively, relative to T1. All statistical comparisons, including the p-values, are presented in Table 2. The dynamic of all IM between time points can be seen summarized in Figure 2(a) or for each IM alone in Figure S3.

$\log_2$FC of T4-IORT (postoperative) relative to T1-IORT (pre-resection): overall impact of surgery and IORT. Seven IMs (IL-1β, IL-6, IL-8, IP-10, MCP-1, MIP-1β, and VEGF) were significantly increased postoperatively within the IORT group. These results are based on testing whether the mean $\log_2$FC values at T4 differed significantly from 0, indicating a true change relative to baseline. Most of these IM showed a distinct upward trend throughout all time points (Figure 2(b)).

$\log_2$FC of T2-IORT (post-resection, pre-IORT) relative to T1-IORT (pre-resection, pre-IORT): effect of

Table 1. Composition of the study and control cohort.

Tumor entities	Total	IORT group	Non-IORT group
All patients	38	18	19
Brain metastases	26	15	11
Malignant melanoma	7	2	5
Non-small-cell adenocarcinoma of the lung	4	3	1
Small-cell carcinoma of the lung	4	3	1
Mamma carcinoma	4	3	1
Squamous cell carcinoma of the lung	3	1	2
Prostate carcinoma	1	1	0
Neuroendocrine carcinoma	1	0	1
Carcinoma of unknown primary	2	2	0
Primary brain tumors	11	3	8
Glioblastoma, IDH wild type (CNS WHO grade **4**)	7	2	5
Astrocytoma, IDH mutant (CNS WHO grade **2**)	1	0	1
Astrocytoma, IDH mutant (CNS WHO grade **4**)	1	0	1
Capillary hemangioma[a]	1	1	0
Atypical meningioma (CNS WHO grade **2**)	1	0	1

[a]In one case, preoperative MRI was highly suggestive of a high-grade primary brain tumor, and even intraoperative frozen section was indicative of a malignant disease. Therefore, IORT was performed. Final histopathological analysis revealed the lesion to be a hemangioma, though.
IDH, isocitrate dehydrogenase; IORT, intraoperative radiotherapy.

surgical manipulation. This comparison aimed to evaluate the immediate effect of tumor resection independent of IORT. Only sCD137 decreased significantly ($p = 0.0367$), suggesting limited IM response due to surgery alone. Again, significance was determined by testing the difference from 0. Notably, none of the IM that later exhibited a significant increase following IORT was significantly affected at this stage.

Difference of T2-IORT (post-resection, pre-IORT) to T3-IORT (post-IORT) as log_2FC relative to T1: No evidence of immediate IORT effect. None of the analyzed IM showed a significant change immediately after IORT. These results are based on testing whether the log_2FC values differed significantly between T2 and T4, indicating a true change in mediator dynamics between these time points. The same approach was applied for the subsequent time point comparisons.

Difference of T2-IORT (post-resection, pre-IORT) to T4-IORT (post-IORT) as log_2FC relative to T1: Evidence of sustained IORT effect. This comparison has the greatest clinical relevance as it assesses the prolonged impact of IORT beyond immediate surgical effects.

Table 2. Comparison of IM levels across all time points: Summary of *p*-values.

Mediator	T1 vs log_2FC of T4	T1 vs log_2FC of T2	log_2FC of T2 vs log_2FC of T3	log_2FC of T2 vs log_2FC of T4	log_2FC of T3 vs log_2FC of T4
EGF	0.1641	0.4102	0.3203	0.4432	0.2330
GM-CSF	0.5633	0.1197	0.2240	0.1457	0.3983
Granzyme	0.7223	0.9326	1.0000	0.6750	0.9442
IFN-γ	0.6103	0.6661	0.6248	0.6103	0.1467
IL-10	0.0546	0.1673	0.8871	0.8506	0.9499
IL-15	0.4185	0.2936	0.1422	0.0759	0.5896
IL-1β	****0.0017**	0.1536	0.4420	***0.0144**	****0.0020**
IL-4	0.5286	0.2622	0.0972	0.1851	0.6726
IL-6	****0.0013**	0.0692	0.3787	****0.0007**	****0.0007**
IL-7	0.5286	0.4469	0.7263	0.9326	0.7998
IL-8	****0.0013**	0.5761	0.4513	****0.0007**	****0.0013**
IP-10	***0.0115**	0.9321	0.7120	****0.0007**	****0.0049**
MCP-1	****0.0020**	0.4513	0.1183	****0.0011**	***0.0135**
MIP-1a	0.0776	0.3433	0.5286	***0.0454**	***0.0294**
MIP-1b	***0.0059**	0.2300	0.2093	****0.0184**	0.0687
PDGF-BB	0.4777	0.3787	0.1323	0.7983	0.1641
sCD137	0.3627	***0.0367**	0.3787	0.2664	0.5049
TNF-α	0.6726	0.2213	0.7223	0.5536	0.5049
VEGF	****0.0059**	0.5895	0.7548	****0.0059**	0.0501

Significant differences are marked in bold and highlighted with stars.
$*p < 0.05$. $**p < 0.01$.
IL, interleukin; IM, inflammatory mediators; IORT, intraoperative radiotherapy; Log2FC, log2 fold change.

Eight IMs (IL-1β, IL-6, IL-8, IP-10, MCP-1, MIP-1α, MIP-1β, and VEGF) increased significantly, showing prolonged IORT-associated immune activation.

Difference of T3-IORT (post-IORT) to T4-IORT (post-operative) as log_2FC relative to T1: Evidence of persistent inflammatory response. The comparison between T3-IORT and T4-IORT aimed to assess the evolution of IM levels over the first postoperative day.

A significant increase was observed in six IMs (IL-1β, IL-6, IL-8, IP-10, MCP-1, and MIP-1α), confirming sustained inflammatory response.

Comparison between the IORT and non-IORT groups

To assess the specific effect of IORT beyond surgical intervention alone, IM profiles were compared between the IORT and non-IORT groups.

Baseline IM levels (T1-IORT vs T1-non-IORT). At the first sampling time point, IM levels were comparable between both groups, confirming no significant baseline differences when including all cancer types or metastases only (Table 3).

Postoperative IM elevation (comparison of log_2FC of T4-IORT vs log_2FC of T4-non-IORT). A key question was whether the IM response at around 24 h

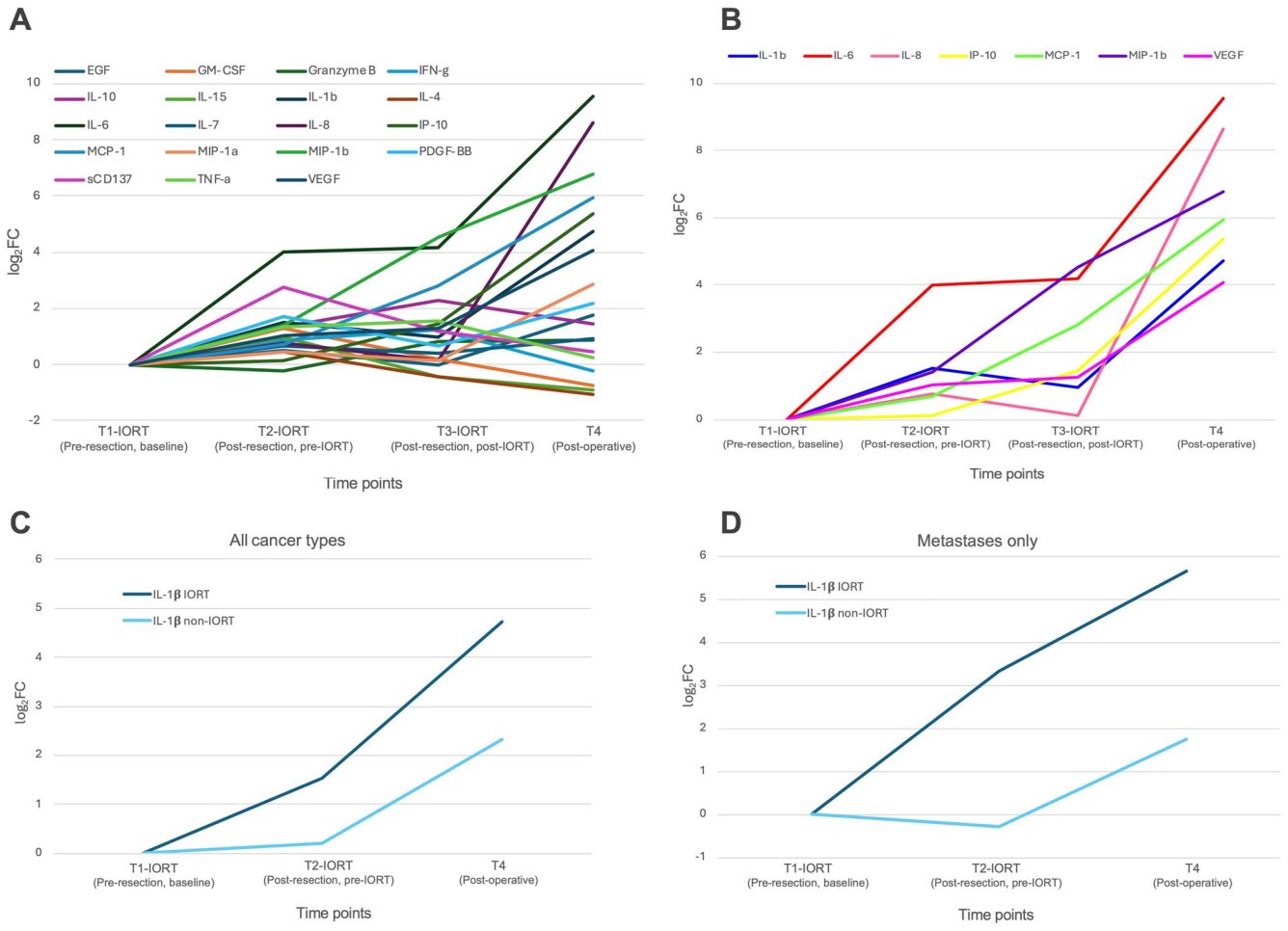

Figure 2. Dynamics of IM after IORT. (a) Log2FC of all analyzed IM across the four perioperative time points in the IORT group. (b) Dynamics of IM showing a significant increase from baseline (T1, pre-resection) to T4 (24 h postoperative) within the IORT group. (c) Comparison of log2FC values for IL-1β between IORT and non-IORT groups, including all tumor entities. (d) Subgroup analysis restricted to patients with brain metastases, showing a significant difference in IL-1β log2FC between IORT and non-IORT groups. IL, interleukin; IM, inflammatory mediator; IORT, intraoperative radiotherapy; Log2FC, $\log_2$ fold change.

postoperatively differed between the two groups. For this purpose, $\log_2$FC values at T4 relative to baseline (T1) were compared between IORT and non-IORT patients. In the overall cohort, no mediator reached statistical significance. However, IL-10 and IL-1β showed a tendency toward higher levels in the IORT group (Table 3; Figure 2(c)). When restricting the analysis to patients with BMs only, thereby reducing cohort heterogeneity, the difference in IL-1β became statistically significant (Table 3; Figure 2(d)).

Postoperative IM elevation excluding pre-frozen samples (comparison of log2FC of T4-IORT vs log2FC of T4-non-IORT). To exclude potential bias introduced by the temporary storage of samples at −20°C, we repeated the postoperative comparison, including only patients with samples that had not been pre-frozen before centrifugation. In total, 17 patients were included in this sensitivity analysis (8 IORT, 9 non-IORT). At T4, VEGF levels were significantly higher in the IORT group compared to the non-IORT group, both in the overall cohort and when restricting the analysis to patients with BMs (Table S4). By contrast, the tendencies observed for IL-10 and IL-1β in the main analysis were no longer apparent. Given the very limited number of available samples, these findings should be interpreted with great caution and cannot provide robust confirmation of the primary results.

Table 3. Statistical comparison of IM changes between IORT and non-IORT for all cancer types and metastases, only when including all samples.

Mediator	All patients		Metastases only	
	Baseline (T1) comparison	Comparison of log_2FC of T4	Baseline (T1) comparison	Comparison of log_2FC of T4
EGF	0.6036	0.2420	0.4809	0.3502
GM-CSF	0.9369	0.2441	0.8058	0.2436
Granzyme B	0.6571	1.0000	0.9470	1.0000
IFN-γ	0.9490	0.6899	0.6572	0.8127
IL-10	0.8894	**0.0800**	0.9161	**0.0577**
IL-15	0.5732	0.6744	0.8943	0.9027
IL-1β	0.5185	**0.1133**	0.6034	***0.0422**
IL-4	0.5435	0.5191	0.9775	0.3970
IL-6	0.6506	0.6376	1.0000	0.8763
IL-7	0.7120	0.7690	0.5499	0.8321
IL-8	0.9485	0.4384	0.4128	0.4363
IP-10	0.8429	0.2420	0.9170	0.4063
MCP-1	0.5702	0.6054	0.5803	0.2326
MIP-1a	0.6219	0.7948	0.3592	0.4490
MIP-1b	0.4102	0.3700	0.6312	0.4675
PDGF-BB	0.6343	0.9394	0.2575	0.6779
sCD137	0.2206	0.2165	0.2708	0.0520
TNF-α	0.2396	0.1800	0.7904	0.2863
VEGF	0.5713	0.9394	0.0759	0.7164

Significance is marked in bold plus a star. Tendencies toward an effect are indicated in bold.
IL, interleukin; IM, inflammatory mediator; IORT, intraoperative radiotherapy; Log2FC, log_2 fold change.

Discussion

RT is a well-established form of local therapy used to treat localized brain tumors.[27] Scientific evidence confirming that radiation induces an immune response against cancer cells is increasing. In addition to direct damage to the cell DNA, RT increases the infiltration of immune cells into the tumor microenvironment and enhances the existing T-cell response with elevation of major histocompatibility complex presentation, resulting in a higher expression and release of multiple IM and other danger signals that activate innate and adaptive immune responses.[28,29]

As a relatively novel alternative RT option, IORT and its influence on the immunological processes within the tumor tissue and surrounding structures are of particular interest. In this context, our prospective study aimed to provide new insights into the immunological effects of IORT in patients with malignant brain tumors by analyzing the profile of IM in the CSF and wound fluid retrieved from the resection cavity at several time points. Our findings indicate that IORT induces a distinct inflammatory response beyond the effects of tissue manipulation through surgical resection alone. This suggests that IORT may

modulate the tumor microenvironment by triggering an acute immunological reaction; however, the clinical effectiveness of such changes remains speculative in the absence of follow-up data. In line with this, recent evidence highlights that systemic inflammatory markers such as the neutrophil-to-lymphocyte ratio and the systemic immune-inflammation index can help to differentiate pseudoprogression from true tumor progression in high-grade gliomas after radiotherapy.[30] This supports the notion that therapy-induced immune shifts may provide clinically relevant information, although further studies are needed to clarify their significance in the context of IORT.

We observed a significant increase in several IMs, including IL-1β, IL-6, IL-8, IP-10, MCP-1, MIP-1β, and VEGF, after IORT compared to baseline levels, with a peak at around 24 h postoperatively. This response is consistent with a previous study that demonstrated that radiation promotes local immune activation and cytokine release, which has been proposed to contribute to antitumor immune responses and tumor recurrence,[16] although this could not be addressed in our study.

Although surgical manipulation alone led to minor changes in IM, the administration of IORT caused a much stronger increase in IM levels.

Previous studies have shown that irradiated dendritic cells secrete more proinflammatory cytokines such as IL-1β,[31,32] which is in line with our results showing a greater increase in IL-1β in the IORT group compared to the control group, reaching statistical significance when restricting the analysis to the more homogeneous cohort of patients with BMs. As a key driver of inflammation and immune cell recruitment, IL-1β has been implicated in tumor progression and resistance to therapy by promoting an immunosuppressive microenvironment.[33] Its marked elevation after IORT suggests a dual role: contributing to an initial inflammatory response that recruits immune cells while inducing immunosuppressive feedback mechanisms via IL-10, which showed a trend toward increased levels in the IORT group. Upon systematic administration of IL-10, immune system activation can be detected. This included elevations in serum granzymes and serum interferon-α.[34] IL-10 induces rejection of tumors and metastases through increased CD8+ T-cell immune responses.[35,36] However, targeting IL-10 failed to yield positive results, as seen with other immune checkpoint inhibition therapies.[37]

Although this study provides valuable new insights into the immunological effects of IORT, its limitations must be acknowledged. The cohort size was relatively small, and larger studies are necessary to confirm the observed trends. Regarding the prescribed radiation dose, different regimens were applied for gliomas (30 Gy) and metastases (20 Gy). Whether there is a dose-dependency of the radiation-induced immune response is not fully understood and cannot be addressed in this study due to the small subgroup of gliomas. Larger sample sizes will hopefully help to better understand the impact of the underlying disease and radiation dose. In addition, the exploratory nature of this analysis and the lack of correction for multiple testing increase the risk of false-positive findings, and the results should therefore be interpreted with appropriate caution. We refrained from applying strict correction methods to avoid missing potentially relevant biological signals in this small exploratory cohort. Furthermore, without long-term follow-up data, it remains unclear how the observed changes in IM translate into clinical outcomes. Some IMs that were significantly elevated after IORT have been linked to tumor progression in other contexts. The observed biomarkers, therefore, remain unvalidated with respect to therapeutic response or prognosis. In addition, potential sources of bias must be considered: group allocation to IORT versus non-IORT was not randomized but decided at the discretion of the interdisciplinary tumor board, which may have introduced selection bias. In addition, the study cohort comprised both primary and secondary brain tumors, which differ in their underlying biology and immune microenvironment. This heterogeneity may have influenced the observed IM response and limited the generalizability of the findings. Moreover, postoperative sample collection was not fully standardized with regard to exact time points, as these were partly dependent on the surgical procedure and perioperative course. Finally, it should be noted that the analyzed samples did not represent pure CSF but also included wound fluid with varying degrees of blood admixture. This may have increased the impact of cell rupture during short-time storage at −20°C. To address this, all analyses were repeated with exclusion of pre-frozen samples. In this restricted cohort, the previously observed effects were no longer

detectable, which is most likely due to the very limited number of patients remaining in the analysis. This underlines that the findings need to be validated in larger and more standardized cohorts to clarify whether the observed immune responses are robust to preanalytical variability.

The key question is whether the observed transient inflammatory response ultimately contributes to improved tumor control or conversely fosters an immunosuppressive environment that could promote recurrence. Longitudinal studies correlating IM dynamics with clinical outcomes such as progression-free and overall survival are essential to determine whether specific IM patterns post-IORT serve as biomarkers for treatment response.

A crucial next step will be to correlate IM dynamics with the composition of peritumoral and residual tissue that remains in situ after resection and is directly exposed to IORT. Histomorphological, immunohistochemical, and potentially molecular analyses of resected specimens could provide valuable insights into the preexisting immune cell composition and tumor microenvironment prior to irradiation. Given that the tumor microenvironment extends beyond the tumor mass itself and influences the surrounding peritumoral tissue, the immune cell populations and signaling pathways identified in the resected specimen may reflect key components of the local immune response in the irradiated field.

Further stratified analyses are needed to understand the differential impact of IORT across tumor types. In particular, it is important to determine whether gliomas, which typically exhibit a more immunosuppressive microenvironment than metastases,[38] show a distinct IM response to IORT. If so, this could indicate that gliomas may require different immunotherapeutic strategies to maximize the benefits of IORT.

Conclusion

This study demonstrated that IORT induces a distinct inflammatory response, with significantly increased IM levels beyond the effects of surgical resection alone. These findings indicate that IORT may modulate the tumor microenvironment, but the clinical significance of these changes remains unclear in the absence of follow-up data. As an exploratory study with a limited sample size, the results should be considered hypothesis-generating. Further research is needed to determine whether these IM alterations impact patient outcomes and whether they can serve as biomarkers for treatment response.

Declarations

Ethics approval and consent to participate

The study was approved by the local ethics committee of the Ludwig-Maximilians-University, which serves as the responsible ethics committee for the Augsburg University Hospital (approval number 22-0554). Consent to participate: Written informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Author contributions

Ehab Shiban: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Supervision; Validation; Writing – original draft.

Philipp Krauss: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Writing – original draft.

Tina Schaller: Data curation; Formal analysis; Methodology; Writing – review & editing.

Ina Konietzko: Investigation; Methodology; Writing – review & editing.

Tatiana Mögele: Conceptualization; Methodology; Writing – review & editing.

Nicola Jungbäck: Investigation; Methodology; Project administration; Writing – review & editing.

Dorothee Mielke: Investigation; Resources; Writing – review & editing.

Bruno Märkl: Conceptualization; Investigation; Supervision; Writing – review & editing.

Klaus-Henning Kahl: Conceptualization; Investigation; Methodology; Writing – review & editing.

Zuzanna Mielewczyk: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Software; Validation; Visualization; Writing – original draft.

Friederike Liesche-Starnecker: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing – original draft.

Acknowledgements

We sincerely thank our medical-technical laboratory assistants, Mrs Juliane Stephan and Mrs Natalia Gerling, for their excellent technical assistance, particularly in sample pre-processing, documentation, and laboratory workflows. We are also grateful to our colleagues from the Department of Neurosurgery for their support with patient recruitment and intraoperative sample collection. Most importantly, we extend our deepest gratitude to the patients who participated in this study. Figure 1 was created using BioRender.com.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Funding for this work was provided by internal funds from the Medical Faculty of the University of Augsburg (project "PRIME TIME"). The funder was not involved in the conduct of the research or preparation of the article.

Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, or publication.

Availability of data and materials

The data generated in this study are available upon request from the corresponding author.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used AI-based text-generation methods (ChatGPT) to optimize, summarize, and translate the text, and to generate the first draft of the manuscript. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Supplemental Material

Supplemental material for this article is available online.

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