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Chapter VI

Intensity-modulated Radiation Therapy in Newly Diagnosed High-grade Gliomas: Potential, Evidence and Perspectives

Dante Amelio, Stefano Lorentini, Marco Schwarz, Maurizio Amichetti
ATreP – Provincial Agency for Proton Therapy, Trento, Italy

Abstract

To date, intensity-modulated radiation therapy (IMRT) is exploited in several types of tumors and has demonstrated the possibility of improving clinical outcomes. Even though it is not the standard radiotherapy approach in the treatment of high-grade gliomas (HGG), it could represent the next step to address the issues that probably still translate into poor therapeutic results. The present chapter points out the unsolved problems dealing with the current radiotherapy treatment approach of HGG and argues why IMRT properties could represent the proper choice. In order to quantify such a benefit, a comprehensive review of the published literature dealing with IMRT in HGG is provided. Finally, we draw some considerations that could either help the large-scale implementation of IMRT in the treatment of HGG or represent new areas of clinical evaluation.

Introduction

High-grade gliomas (HGG) are the most common primary brain tumors in adults and represent approximately 2% of all cancer diagnoses [1].

In the 2007 World Health Organization (WHO) classification they are recorded as tumors of the neuroepithelial tissue: in fact, their histologic features mirror those of the mature glial cells [2].

The acronym HGG includes anaplastic astrocytoma (AA) - WHO grade III, and glioblastoma multiforme (GBM) - WHO grade IV. The former generally occurs during young to middle adulthood while the incidence rate of the latter increases with advancing age but decreases over 85 years [3].

HGG are featured by a very aggressive behavior and despite the availability of multimodality treatments the prognosis remains dismal. Overall, the median survival for GBM patients ranges between 12 and 15 months [4] whereas it is approximately 3 years for patients harboring AA [5]. Even if survival strongly depends on the histologic subtype, the recursive partitioning analysis (RPA) from the Radiation Therapy Oncology Group (RTOG) pointed out the prognostic role played also by different factors such as age, Karnofsky Performance Status (KPS), extent of resection, post-surgical neurological deterioration, patient condition before radiotherapy (RT) and delivered radiation dose [6]. Moreover, researchers are looking for both molecular and genetic markers with an impact on prognosis. After about 20 years of research, evidence does not support the usefulness of p53 mutation and expression [7] while, at least in GBM, the beneficial role of O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation seems to be clear [8]. Finally, interesting results suggest a potential influence also for epidermal growth factor receptor (EGFR) [9], 1p/19q alterations [10] and mutations of isocitrate dehydrogenase (IDH) [11].

To date, the standard of care is represented by a multimodality approach including surgical resection to the extent feasible, adjuvant RT and chemotherapy (CHT).

Despite a relatively high number of prospective and retrospective studies, the issue whether the extent of surgical resection has a significant influence on HGG survival is still debated. However, sufficient data exists to support a class II evidence and to recommend the maximal safe resection [12] as the first step in the management of such patients.

Radiotherapy is an integral part of the standard of care of HGG. Of all the treatment modalities, it demonstrated the greatest influence on HGG survival with a class I evidence [13]. Since long time radiation oncologists did also address several issues as the use of non-conventional fractionations [14], dose intensification [15] and use of different delivery techniques [16, 17] but failed to provide a significant clinical benefit over the standard regimen. To date, RT is usually delivered with three-dimensional conformal techniques, in 1.8–2 Gy per fraction to a total dose of 59.4–60 Gy.

The delineation of clinical target volume is still controversial [18]. The European Organization of Research and Treatment of Cancer (EORTC) suggests the area to be irradiated is represented by tumor bed/resection cavity and any area of contrast enhancement with a 2-3 cm margin. In contrast, current RTOG guidelines suggest a two-steps targeting: at the beginning, an area defined as post-operative T2 hyperintensity + 2-2.5 cm margin receive 46-50 Gy followed by an additional 14-10 Gy boost to the area of contrast enhancement + 2-2.5 cm. In order to accomplish this task the co-registration of conventional magnetic resonance (MR) images with treatment planning computed tomography (CT) is strongly suggested so that an accurate definition of both the tumor and the nearby organs at risk (OARs) can be guaranteed. From this standpoint, new MR imaging modalities as well as

positron emission tomography (PET) imaging can ameliorate the tumor visualization and may represent an interesting approach to further improve the treatment planning accuracy.

While the evidence regarding RT in HGG does not show differences with regard of histologic subtype, data about CHT administration are not consistent. Before the introduction of the oral alkylating agent temozolomide (TMZ) in the treatment of HGG, the addition of CHT was a controversial issue: single small prospective trials failed to demonstrate a reliable survival benefit; conversely, a meta-analysis pooling these series did suggest such benefit regardless of the histology [19]. This study also included the data from the largest randomized trial of adjuvant CHT for HGG that, however, pointed out no survival and progression-free survival benefit to CHT [5]. More recently, the phase III randomized trial promoted by EORTC and the National Cancer Institute of Canada (NCIC) has shown unequivocally the survival advantage conferred by combined treatment (RT plus concomitant and adjuvant TMZ) with respect to radiation alone in GBM patients [4]. However, even though TMZ demonstrated activity also in patients with AA, level I evidence for a survival benefit does not exist. Thus, the current standard of care for newly diagnosed GBM is radio-chemotherapy according to the EORTC/NCIC trial following maximal safe resection while newly diagnosed AA should receive postoperative RT only. However, it is noteworthy that the conventional RT-TMZ schedule is widely adopted also in the management of newly diagnosed AA. The last consideration regards the NOA-04 phase III randomized trial that recently compared efficacy and safety of RT followed by CHT (procarbazine-vincristine-lomustine or TMZ) at progression with the reverse sequence in patients with newly diagnosed anaplastic gliomas [20]. The results demonstrated the feasibility of initiating postoperative treatment with either CHT or RT in patients with anaplastic gliomas. Although no differences in time to treatment failure or progression-free survival (PFS) were demonstrated between initial RT and initial CHT, in the AA subgroup, PFS was 10.8 months with RT and 18.2 months with CHT. These data may allow to recommend CHT as first-line treatment of patients with anaplastic gliomas, including patients with AA, postponing RT at recurrence [20].

After several decades of research a general consensus regarding the standard of care of HGG has been reached and the overall knowledge on these malignancies is continuously increasing thank to the new discoveries dealing with genomics, proteomics, diagnostic imaging, surgical technique and chemotherapy agents. These advances should hopefully translate in a further increase of long-term survivors even though a disappointing rise in radiation-related late side effects could be observed in patients with extended survival. However, the life expectancy (especially for GBM patients) is still unsatisfactory even in the TMZ-age, with mortality given primarily from local tumor relapse/progression in or adjacent to the resection cavity [21]. In fact, extracranial metastases are rare, and relapses up to several centimeters away from the tumor are infrequent and delayed. Such considerations suggest that improving local control may prolong overall survival and certainly encourage further efforts to improve the RT delivery. Intensity-modulated radiation therapy (IMRT) is now widely used in the treatment of several different tumors for its ability to improve dose conformity and spare critical neighboring normal tissues when compared with conventional radiotherapy. From this standpoint, it could represent a new tool to improve the therapeutic ratio in the treatment of HGG.

Potential

As stated above, photon radiotherapy is a mainstay of the treatment of HGG. By far the most employed technique is three-dimensional conformal radiotherapy (3D-CRT). The goal of 3D-CRT is to conform the spatial dose distribution to the 3D target volume (usually represented by tumor, areas at risk of involvement/infiltration plus a margin for uncertainties). This task is accomplished using a set of uniform intensity fixed beams shaped on the target. The rationale is to best optimize the target dose while sparing adjacent normal tissues.

Despite the overall improvement of 3D-CRT in comparison with older 2D techniques, there are clinical scenarios with large and/or complex shaped lesions, and/or located in critical areas for which the delivery of a safe dose to OARs is achieved at the price of an insufficient dose to the target. In order to overcome these drawbacks, IMRT has been developed as an evolutionary and advanced form of 3D-CRT: the modulation of the photon fluence results in a non-uniform dose within the treatment fields [22,23]. Thanks to a computer-based optimization of the photon fluence used to treat the patient, with IMRT it is possible to generate very homogenous and concave dose distributions along with high conformity, improving target coverage as well as OARs sparing.

These brief considerations depict IMRT as a very pliant technique. In the context of HGG, these potentials can fit with several tumor features providing a new tool to address unsolved issues. As a consequence, both primary and secondary clinical endpoints could get a benefit.

Towards the Improvement of Target Coverage and Healthy Tissues Sparing

HGG are intra-axial malignancies that can develop everywhere across the brain. Therefore, the proximity with OARs such as optical pathways, ocular globes and brainstem can vary widely: while some lesions lie far from any OARs, others can be very close even to three healthy structures at the same time. It is important to remember that the OARs in HGG are usually structures that can be damaged even if just a small portion of the volume is irradiated at high doses, and that toxicity to this structure has a very severe impact on patient's quality of life. Moreover, apart from the proximity to the OARs, HGG are tumors in which the radiographically apparent tumor volume (containing mainly malignant cells) co-exists with a sub-clinical and difficult-to-detect infiltrating tumor component (mainly containing normal glial cells). There is general consensus on attempting to include such component within the target volume even though simply by an isotropic expansion of the gross tumor volume. This safety margin is typically of 2-3 cm, so the volume to be treated is very often huge, either approaching or exceeding the totality of a brain lobe, and ultimately influencing the radiation related toxicity. This means that, even when the target volume is a nearly spherical shaped, and therefore conformity is quite easily achieved, a certain amount of healthy brain tissue is always irradiated.

These considerations clearly suggest that achieving adequate target coverage while sparing OARs can be challenging in HGG patients. Furthermore, apart from theoretical remarks, the quality assurance article regarding the randomized phase III EORTC/NCIC trial clearly demonstrated as this issue represents a real pitfall in the clinical practice. Ataman et al. [24] pointed out that planning target volume (PTV) under-dosage (< 95% of the prescribed dose) was observed in 39% of the participating centres while in 19% of the patients, field sizes were reduced in the effort to decrease the dose to adjacent critical structures. The homogeneity within the PTV was outside the recommended range in 33% of the centres. Finally, the maximum dose limit to brainstem and chiasm was violated in 24% and 19% of the patients, respectively. It is noteworthy that, overall, in 55% of patients the tumor was located in the temporal or frontal region, where there is a high likelihood to get relationship with optical pathways and/or brainstem.

In this scenario, where at least in a sub-group of patients the use of conventional 3D-CRT may result in unacceptable dose delivery to target and/or OARs, the use of IMRT should be considered, as even in presence of one or more dose-limiting OARs the target coverage could be improved without worsening the risk of toxicity. In HGG, where the majority of cases continue to recur in the immediate proximity of the primary tumor, a better tumor coverage could translate into the amelioration of local control, if just by prolonging the time to recurrence and the PFS.

At the same time, even for patients where achieving an adequate coverage is not of concern due to the absence of dose-limiting OARs, the use of IMRT could reduce the dose to the healthy brain ultimately decreasing both early and late radiation related toxicity and potentially improving quality of life (QoL). Hottinger et al. [25] recently reviewed the GBM treated at Memorial Sloan-Kettering Cancer Center between 2001 and 2003: they pointed out a median survival of 9 years in 11% of cases. Twenty-eight percent of them had clinically significant radiation-induced leukoencephalopathy, 23% developed radionecrosis and 23% treatment-related strokes. These data clearly show how such issue is becoming relevant in HGG and encourage further efforts to exploit the IMRT potential.

Harnessing a "New" Technique to (re)Test an Old Concept

Basic radiobiological considerations suggest that hypofractionated RT with large fraction size is effective for tumors with low α/β ratio. In this scenario, employing a large dose per fraction with the same biologically equivalent dose (BED) of conventional fractionation would achieve similar tumor control probability, reduce the overall treatment time and possibly increase the risk of late toxicity.

Although HGG are supposed to have a high α/β ratio, few reports deal with this issue and data are not consistent. For instance, Raaphorst et al. [26] showed a large 'shoulder' in survival curves of *in vitro* malignant gliomas cell lines that suggests a low α/β ratio. An *in vivo* study reports that hypofractionation demonstrated the most prominent tumor regression compared both to hyperfractionation and to conventional fractionation [27]. Moreover, several clinical series employing accelerated hyperfractionated RT (usually exploited to overcome the accelerated tumor cell repopulation) failed to demonstrate a survival benefit

[28]. These results suggest a low α/β ratio for HGG. As a consequence, considering the cell killing increase, hypofractionated regimens would be more apt to treat such tumors.

Actually, treating HGG by hypofractionation is not a new concept: since the eighties, three randomized phase III and several prospective phase I or II studies have been published on this subject [14]. However, most of them included only the subset of patients with poor prognosis. The rationale behind this policy includes reducing the overall treatment time, delivering a well tolerated and effective schedule without the concern of late neurological sequelae because of the shorter life expectancy. Despite the results have demonstrated that hypofractionation is feasible, well tolerated and as effective as conventional regimen in poor prognosis HGG, the concern for cognitive impairment and radionecrosis ultimately hindered assessing its role in patients with good prognosis.

The high conformity and homogeneity levels achievable with IMRT can reduce the risk of radiation-related toxicity and therefore allow addressing again this issue. Moreover, (re)exploring hypofractionation in HGG best fits with a further unique application of IMRT, i.e. the so-called simultaneous-integrated-boost (SIB) technique. This delivery method allows planning and irradiation of different dose levels to different targets in the same treatment session. As a consequence, SIB IMRT can deposit a dose gradient between regions of gross tumor involvement and regions at risk for microscopic tumor infiltration: normal tissues will receive a conventional dose level avoiding higher toxicity rates while a higher dose per fraction delivered to the primary target along with an overall BED increase may improve the tumor control probability. Even if, so far, clinical results about dose escalation have demonstrated neither an improvement of primary endpoints nor changes in pattern of failure regardless of the delivery technique [15-17], the above mentioned considerations suggest that hypofractionation itself may have a greater biological effect on glioma cells. Therefore, SIB IMRT seems the natural choice to pursue improvement in local tumor control by the combination of hypofractionation and dose escalation. However, this strategy also carries a theoretical disadvantage: it is unclear whether aggressive dose escalation in the context of concurrent use of TMZ can increase the incidence of the overall treatment related toxicity and radionecrosis.

Finally, it is noteworthy that applying a SIB technique leads to a further advantage: the shortening of the overall treatment time, that seems more appropriate in relation to the short life expectancy of HGG patients.

Evidence

Since the early nineties IMRT has been used to treat several types of tumors in different anatomical regions. Its capability of carving the dose around the structures and the steep dose gradients allowed to spare several OARs such as rectum and small bowel in prostate cancer [29], or spinal cord, brainstem, optical pathways, parotid glands and inner ear in head and neck tumors [30], the two most treated tumors with IMRT. Moreover, IMRT has been employed in several other tumors with encouraging results [31-36]. Veldeman et al. [37] recently investigated the evidence levels supporting the routine use of IMRT for various disease sites in terms of overall survival (OS), disease-specific survival, QoL, treatment-

induced toxicity or surrogate endpoints. Their systematic review pointed out a reduced toxicity for various tumor sites by using of IMRT whilst findings regarding primary clinical endpoints were generally inconclusive.

Even though IMRT is now considered a feasible and practical delivery technique, to date it is not the standard radiotherapy approach in the treatment of HGG. Several publications exist concerning the overall influence of IMRT in such malignancies. However, both dosimetrical and clinical results are not always consistent and the question whether IMRT has a relevant advantage over 3D-CRT is still unanswered.

This chapter section provides a comprehensive review of the published literature dealing with this issue.

Dosimetrical Studies

Several treatment planning studies were proposed over the last decade, dealing with the best approach to manage the irradiation of HGG patients. The majority could be referred as planning studies comparing either 3D-CRT vs IMRT [38-44] and/or different IMRT techniques such as static field-IMRT with and without SIB, volumetric arc therapy (VMAT) and helical Tomotherapy (HT) [42,43,45,46]. A summary of the planning studies characteristics is shown in Table 1. It's noteworthy how a wide variability in terms of kind of lesions, dimensions, positions, fields' arrangement, treatment dose prescription and planning software is present.

As far targets and healthy tissues can not be considered as two different entities within a treatment plan, these studies can be better understood by analysing separately the results for target volumes and OARs.

1) Target Volumes

a) Dose Coverage

The vast majority of data coming from planning studies suggest that IMRT and 3D-CRT provide similar PTV coverage. Only one work (Thilmann et al. [38]) showed noticeable differences between 3D-CRT and IMRT, which were quite large for the primary PTV (13.1% benefit in V95% from IMRT) and smaller for the boost volume, where IMRT did actually worse than 3D-CRT (V95% of 93.7% for 3D-CRT vs 87.5% for IMRT). Among the studies comparing different IMRT techniques, only Wagner et al. [42] found some differences in term of target coverage, in favour of VMAT.

b) Dose Homogeneity

Information about target dose homogeneity is not available for all dosimetrical studies and, in addition, the metrics to evaluate this parameter change from study to study. Having said that, there is some level of agreement among studies on this matter, i.e. IMRT is associated to a dose homogeneity which is always at least as good as, and often better than, that achieved by 3D-CRT plans.

Table 1. Main characteristics of the treatment planning studies concerning IMRT in high-grade gliomas

Authors	No. of patients	Prescription & Fractionation	Site of lesions	Volumes
Thilmann et al. [38]	20	3D-CRT: 60 Gy to PTV2 and 75 Gy to PTV1 – SIB in 30 fx IMRT: same as 3D-CRT	N/S	PTV2: mean (263 ± 106) cc PTV1: mean (51 ± 37) cc
Chan et al. [39]	5	3D-CRT: 59.4 Gy to PTV in 33 fx IMRT: 59.4 Gy to PTV and 70 Gy to GTV–SIB in 33fx	N/S	GTV: mean 58 cc; range (29-118)cc PTV: mean 361 cc; range (266-427) cc
Narayana et al. [44]	20	3D-CRT: 59.4-60 Gy (1.8-2 Gy/fx) IMRT: same as CRT	N/S	N/S
MacDonald et al. [47]	20	3D-CRT: 45 Gy to PTV+ 14.4 Gy to PTVboost (1.8 Gy/fx) IMRT: same as 3D-CRT	11 frontal, 9 temporal or occipital	N/S
Hermanto et al. [40]	20	3D-CRT: 50 Gy to PTV + 10 Gy to PTVboost (2Gy/fx) IMRT: 50 Gy to PTV and 60 Gy to PTVboost – 30 fx with SIB	8 frontal, 8 parietal, 4 temporal	GTV: mean (90 ± 54) cc range (180-763) cc PTV: mean (347 ± 137) cc; range (18-273) cc
Piroth et al. [41]	16	3D-CRT: 60 Gy to PTV (2 Gy/fx) + 12 Gy to PTVboost (2.4 Gy/fx) – Concomitant Boost IMRT: 60 Gy to PTV (2 Gy/fx) and 72 Gy to PTVboost (2.4 Gy/fx) - SIB	8 frontal, 4 temporal, 4 parietal; 8 in right side and 8 in left side. No overlaps with OARs	PTVboost: mean (12.1±18.6) cc PTV: mean (175.2±54.4) cc
Suzuki et al. [45]	4	IMRT *: 70 Gy to GTV (2.5 Gy/fx) and 56 Gy to surrounding edema (2 Gy/fx) – SIB	3 parietal, 1 temporal	GTV: mean: 87.7cc; range (43.1-188) cc CTV: mean: 326.65 cc; range (205.8 -553) cc
Wagner et al. [42]	14	3D-CRT: 59.4 Gy to PTV (1.8 Gy/fx) IMRT: 60 Gy to PTV (2Gy/fx) VMAT: same as IMRT	N/S	PTV: mean 432.9 cc; range (310.9–815.2) cc

Zach et al. [43]	20	3D-CRT: 46 Gy to PTV + 14 Gy to PTVboost (2 Gy/fx) IMRT: same as 3D-CRT SIB-IMRT: 46 Gy to PTV (2 Gy/fx) and 53.8 Gy to PTVboost (2.34 Gy/fx) - SIB HT: same as SIB-IMRT	N/S	PTVboost: mean 300 cc; range (137-567) cc PTV: mean 452 cc; range (276-1074) cc
Shaffer et al. [46]	10	IMRT: 60 Gy to PTV (2 Gy/fx) VMAT: same as IMRT	N/S; overlaps with OARs	PTV: mean 343 cc

Legend. 3D-CRT: Three Dimensional Conformal Radiation Therapy; IMRT: Intensity-Modulated Radiation Therapy; VMAT: Volumetric Modulated Arc Therapy; HT: Helical Tomotherapy; fx: fraction; SIB: Simultaneous Integrated Boost; N/S: Not Specified; GTV: Gross Tumour Volume; PTV: Planning Target Volume.

* Comparison between overlapping structure-based and non-overlapping structure-based optimization methods.

Five papers provide specific figures on dose homogeneity.

Hermanto et al. [40] found a small difference in favour of IMRT in the PTV and even a smaller one in the boost volume.

Piroth et al. [41] showed a significant improvement in IMRT with respect to 3D-CRT for both the PTV and the boost volume. Zach et al. [43] found similar results as Piroth et al. and, in addition, by comparing different IMRT techniques, report that HT achieves the best dose homogeneity in the target volume. In another comparison among IMRT techniques [42], static-field IMRT obtained more homogeneous target dose than VMAT, a result which is not confirmed by a similar study (Shaffer et al. [46]).

The remaining studies we analyzed [38,39,44,45,47] didn't provide a dedicated index for homogeneity assessment, but it could be estimated through Dmin and Dmax figures. Nevertheless, no large differences are pointed out between IMRT and 3D-CRT.

c) Dose Conformity

Similarly to dose homogeneity, the parameter to evaluate dose conformity is not unique among the planning studies. However, all works show that IMRT improves target dose conformity.

The most commonly used parameter to evaluate the conformity is the conformity index (CI). All studies using this metric, though with a slight different implementation [40-42,46] always found differences in favour of IMRT which, in some cases (e.g. Piroth et al. [41]) were statistically significant.

The same applies to Thilmann et al. [38] who, estimating the dose conformity according to Baltas et al. [48], found a better value for IMRT both for the primary PTV and for the boost volume, achieving statistically significant difference.

2) Organs at Risk

As mentioned above, the anatomical regions at risk, typically considered in HGG patients, are brainstem, optic pathways (chiasm and optic nerves), lens, and retina. Since the

toxicity endpoint for these OARs is typically considered as a 'serial' kind of complication, the most relevant dose parameter to be evaluated is the maximum dose. In general, IMRT allowed better organs at risk sparing than 3D-CRT, although to an extent that varies considerably from study to study.

In addition to these 'primary' OARs, most studies compared different irradiation techniques on a number of other normal tissues. MacDonald et al. [47] showed that IMRT allows reducing Dmax in the cochlea by some percentage points (even if not statistically significant), while Narayana et al. [44] found similar results for the ocular globe, where IMRT achieved some degree of sparing with respect to 3D-CRT. Zach et al. [43] assessed ocular globe irradiation through the Dmax value, obtaining a small dose sparing of the ipsilateral ocular globe with HT with respect to IMRT and a slightly larger benefit with respect to 3D-CRT. The contrary applies to the contralateral globe, with maximum doses being highest for HT and smallest for 3D-CRT, though these techniques do not achieve irradiation levels of potential clinical concern.

The healthy brain irradiation is an unavoidable consequence of the treatment, thus representing an interesting issue also from the dosimetrical point of view. Most studies available in the literature provide data on the irradiation levels for the healthy brain, although there are inconsistencies in the definition of both the region of interest and the relevant dosimetric indices. In general, the dose region ranging from 0 to 30-40 Gy is the most analysed.

Chan et al. [39] showed a 5 Gy reduction in normal brain mean dose from 32 Gy to 27 Gy thanks to IMRT. Thilmann et al. [38] reported not statistically significant differences in mean dose, but a large reduction of V50 (from 60% to 33%, $p<0.001$) and a very small reduction of V30 (from 253 cc to 242 cc, $p<0.2$) for the normal brain defined as cerebrum plus cerebellum and brainstem minus PTV.

In three studies [44,46,47] the normal brain was defined as brain minus PTV. Narayana et al. [44] showed that IMRT is associated with a reduction of Dmean by about 2 Gy, of V18 by about 7% and of V24 by about 8%; all differences being statistically significant. MacDonald et al. [47] scored V18, V24 and V45, showing that IMRT reduces the irradiated volume by 10%, 15% and 40%, respectively, at a statistically significant level. No differences were apparent at higher doses. Shaffer et al. [46], comparing VMAT with static-fields IMRT, showed a 12% reduction in mean dose in favour of VMAT and no difference in Dmax. Hermanto et al. [40] assessed the integral dose (ID) to the normal brain, highlighting the differences between IMRT and 3D-CRT in two different volumes: *brain minus PTV*, where the mean dose decreased from 21.3 Gy to 19.1 Gy with IMRT, and *brain minus GTV*, where IMRT allowed for a dose reduction of about 3 Gy. This dose reduction was statistically significant for both volumes studied.

Among all the studies showing a better brain sparing by IMRT there is, however, an exception: Piroth et al. [41] showed some increase in mean dose to normal brain tissue using IMRT (25.6 Gy vs 22.9 Gy with 3D-CRT). Unfortunately, no information are provided on how the brain tissue was defined.

In a study where SIB-IMRT was tested (Suzuki et al. [45]) on two different scenarios, Dmean and $D_{5\%}$ were scored to assess normal brain irradiation. Dmean for IMRT based on the first configuration (26.8 Gy) was significantly higher than that supplied by IMRT based on the second one (26 Gy), while for $D_{5\%}$ not statistically significant differences were shown.

Finally, Zach et al. [43] compared different IMRT techniques and assessed the dose to the normal brain (defined as *brain tissue minus PTVs*) through $D_{10\%}$, $D_{50\%}$ and $D_{90\%}$. HT obtained consistently better results on $D_{10\%}$ than 3D-CRT and IMRT; for $D_{50\%}$ and $D_{90\%}$ IMRT and 3D-CRT were superior to HT, although no significant differences in the integral dose to the normal brain was found among all the plans.

Even though not directly related to HGG disease, also a recent work [49] designed to look into the potential dosimetric advantages of IMRT for whole ventricles irradiation, shows a significant spare of healthy brain in the dose region ranging from 1 to 24 Gy, up to a maximum of 10%, using IMRT with respect to 3D-CRT.

From the planning point of view, a critical situation is represented by that one where overlaps between PTV and organs at risk occur. In this case the dosimetric results provided by the different techniques can dramatically change as a function of the complexity of these overlaps. Preliminary results obtained by two studies addressing the PTV-OARs superposition (Follwell et al. [50] and Lorentini et al. [51]) suggest that IMRT can do significantly better than 3D-CRT in complex gliomas adjacent to healthy structures.

In one case [51] the changes in target coverage have been systematically evaluated as a function of the number of OARs at risk overlapped with PTV, starting from 0 up to 4 different structures (i.e. brainstem, optic chiasm, optic nerves, cochlea).

By design, both 3D-CRT and IMRT fulfilled the OARs constraints and they ended up providing similar dose conformity and homogeneity, regardless of the number of overlapping OARs. Concerning target coverage, a trend showing better IMRT results emerged with 2 overlapping OARs and became significant when 3 or more OARs extend over PTV (as shown in Figure 1). It is noteworthy that when 2 OARs overlapped with PTV, 3D-CRT plans were far from achieving satisfactory target coverage [51].

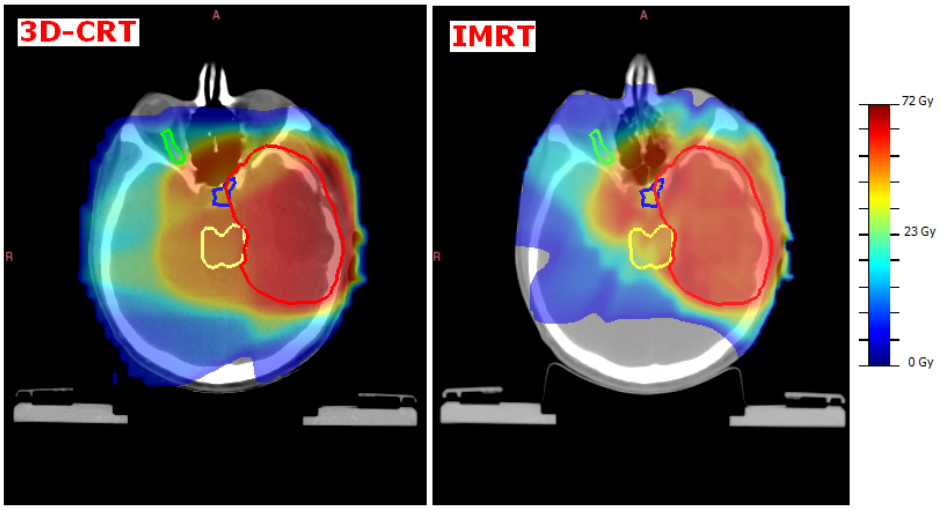

Figure 1. Comparison between 2D dose distributions produced by 3D-CRT and IMRT plans, respectively. One can see the better dose conformity around PTV (red) provided by IMRT as well as an improved avoidance of the brainstem. Furthermore, IMRT allows to reduce the healthy brain dose with respect to 3D-CRT. The high dose region outside of the target is due to the changing shape of PTV in the neighbouring slices of the CT scan.

Table 2. Main series regarding the treatment of high-grade gliomas with IMRT: patient charateristics, treatment features and clinical outcomes

Study	No. of pts	Med Age	PS score (%)	Surgery (%)	RT Tot.dose/dpfx in Gy BED°	CHT	% OS*	% PFS*	Acute Tox. %	Late Tox. %	Rad. Nec.	Med F/U
Narayana et al. [44]	58	54	2 med	G (46) S (28) B (26)	PTV1 (GD+1.5cm+5mm SM) 59.4-60/1.8-2 BED 70-72	46	1 yr 30 2 yr 0 med 9	1 yr 0 2 yr 0 med 2.5	G1-2 36 G3 7 G4 3	G1-2 7 G3 3	None	24
Fuller et al. [58]	31	63	N/R	G (30) S (51) B (19)	PTV1 (GD+edema+2cm +2-3mm SM) 45-46/1.8-2 BED 53-55 PTV2 (CE+1cm+2-3mm SM) 59.4-60/1.8-2 BED 70-72	16	1 yr - 2 yr - med -	1 yr - 2 yr - med 7.3	G1-2 70 G 3 12	N/R	N/R	N/R
Sultanem et al. [54]	25	55	0 (24) 1 (60) 2 (16)	G (24) S (44) B (32)	PTV1 (CE+1.5cm) 60/3 BED 78	0	1 yr 40 2 yr – med 9.5	1 yr - 2 yr - med 5.2	None	Visual loss 4	None	8.8
Floyd et al. [55]	20	60	0/1 (100)	N/R	PTV1 (edema+SM) 30/3 (SIB) BED 39 PTV2 (CE+SM) 50/5 (SIB)	0	1 yr - 2 yr - med 7	1 yr - 2 yr - med 6	G1 5	G2 13 G4 20	20	N/R

					BED 75							
Iuchi et al. [56]	25	62	2 med	G (48) S/B (52)	PTV1 (edema) 32/4 (SIB) BED 45 PTV2 (PTV3+1.5cm) 40/5 (SIB) BED 60 PTV3 (CE+5mm) 48 to 68/6 to 8.5 (SIB) BED 77 to 126	19	1 yr 71 2 yr 56 med -	1 yr 71 2 yr 54 med -	G1 4	Bleeding/infarction 8	12	11
Nakamatsu et al. [57]	13	56	0 (15) 1 (31) 2 (54)	G (62) S (23) B (15)	PTV1 (GD+2cm +5mm SM – PTV2) 56/2 (SIB) BED 67 PTV2 (GD+5mm SM) 70/2.5 (SIB) BED 87	11	1 yr 75 2 yr 25 med -	1 yr 25 2 yr 13 med 8	G1-2 31	None	None	17
Monjazeb et al. [53]	21	56	0/1 (100)	G (38) S (43) B (19)	PTV1 (GD+edema+1cm) 50.4/1.8 BED 59 PTV2 (CE+5mm) 70 to 80/2.5 BED 87 to 100	0	1 yr 57 2 yr 19 med 13.6	1 yr - 2 yr - med 6.5	G1-2 100 G3 38 G4 5	G1-2 62 G3 9	None	N/R

Table 2. Continued

Panet-Raymond et al. [59]	35	63	N/R	G (37) S (37) B (26)	PTV1 (CE+1.5cm) 60/3 BED 78	29	1 yr - 2 yr - med 14.4	1yr - 2 yr - med 7.7	N/R	N/R	N/R	12.6
Morganti et al. [52]	19	59	0 (47) 1 (21) 2 (32)	G (63) S (32) B (5)	PTV1 (GD+edema+2cm +5mm SM) 45/1.8 (SIB) BED 53 PTV2 (CE+1cm+5mm SM) 60 to 64/2.4 to 2.6 (SIB) BED 74 to 82	19	1 yr 82 2 yr 29 med 20	1 yr 49 2 yr – med 12	G1-2 58	G1-2 10	None	23
Cho et al. [60]	40	54	0 (3) 1 (75) 2 (20) 3 (3)	G (46) S (18) B (36)	PTV1 (edema+1cm +3-5mm SM) 50/2 BED 60 PTV2 (CE+3-5mm SM) 60/2.4 BED 74	21	1 yr 64 2 yr 42 med 14.8	1 yr 46 2 yr 31 med 11	G1-2 25	G1-2 15 G3 3	8	13.4

Legend. No.: number; pts: patients; PS: performance status (according ECOG-WHO-Zubrod); RT: radiotherapy; CHT: chemotherapy; F/U: follow-up; OS: overall survival; PFS: progression-free survival; med: median; G: gross; S: subtotal; B: biopsy; N/R: not reported; BED: biologically effective dose; °: α/β ratio = 10 Gy; effective doubling time = 5 days; kickoff time for accelerated repopulation = 14 days; *: median in months; Tox.: toxicity; Rad. Nec.: radiation necrosis; PTV: planning target volume; yr: year; GD: gross disease; CE: contrast enhancement; SM: setup margin; G: grade; dpfx: dose per fraction; SIB: simultaneous integrated boost.

Table 3. Reference studies concerning conventional radiotherapy +/- chemotherapy in good-prognosis high-grade gliomas: patients, treatment features, clinical outcomes and radiation-related toxicities

Study	No. of pts	Med Age	PS score (%)	Surgery (%)	RT Tot.dose/dpfx in Gy BED°	CHT	% OS*	% PFS*	Acute Tox. %	Late Tox. %	Rad. Nec.	Med F/U
Stewart [19] RT	1306	<60 yrs 72%	Good 45 Poor 34	G 24 S 55 B 18	40 to 60/1.8-2 BED 54 to 72	/	1 yr 40 2 yr 15 med -	1 yr - 2 yr - med 6	N/R	N/R	N/R	24
RT+CHT	1698	<60 yrs 71%	Good 37 Poor 33	G 25 S 56 B 16	40 to 60/1.8-2 BED 54 to 72	NU	1 yr 46 2 yr 20 med -	1 yr - 2 yr 15 med 7.5	N/R	N/R	N/R	24
Stupp et al. [61] RT	286	57*	0 38 1 49 2 12	G 40 S 45 B 16	60/2 BED 72	/	1 yr 51* 2 yr 11 med 12.1	1 yr 9* 2 yr 2 med 5	G2 48* G3-4 10*	G3-4 0.3 fatigue	N/R	61
RT+TMZ	287	56*	0 39 1 47 2 13	G 39 S 44 B 17	60/2 BED 72	TMZ	1 yr 61* 2 yr 27 med 14.6	1 yr 27* 2 yr 11 med 6.9	G2 70* G3-4 15*	G3-4 1 visual deficit, seizure	N/R	61
Slotman et al. [62]	30	56	0 0 1 50 2 44	G 40 S 54 B 7	42/3 BED 55	None	1 yr 24 2 yr - med 8.4	1 yr - 2 yr - med 5.8	G3-4 0	G3-4 0	0	24

Table 3. Continued

Lang et al. [63]	38	58 (mean)	N/R	G 0 S 76 B 24	42/3.5 BED 57	None	1 yr 34 2 yr - med 10.6	1 yr - 2 yr - med -	G3-4 0	G3-4 0	0	N/R
Arslan et al. [64]	20	57	0-2 57	G 50 S 25 B 25	50/3.33 BED 67	None	1 yr 50 2 yr - med 12	1 yr - 2 yr - mean 6.8	G3-4 0	G3-4 5	5	10 (mean)

Legend. No.: number; pts: patients; PS: performance status (according to ECOG-WHO-Zubrod); dpfx: dose per fraction; BED: biologically effective dose; RT: radiotherapy; CHT: chemotherapy; OS: overall survival; PFS: progression-free survival; med: median; G: gross; S: subtotal; B: biopsy; N/R: not reported; TMZ: temozolomide; NU: nitrosoureas; yr: year; yrs: years; F/U: follow-up; Rad. Nec.: radiation necrosis; Med.: median; G: grade; °:α/β ratio = 10 Gy; effective doubling time = 5 days; kickoff time for accelerated repopulation = 14 days.

* Data from Stupp et al. 2005 [4] because not reported in the updated report [61] (median in months).

These results point out that IMRT is a superior technique to 3D-CRT in particular when there are overlaps between OARs and PTV. In these situations IMRT allowed for a better target coverage maintaining at the same time equivalent or better OARs sparing. These data suggest that the overlap of three OARs can be used as a dosimetrical criterion to select which patients should receive IMRT.

Clinical Series

To date, the medical literature dealing with the use of IMRT in newly diagnosed HGG is fairly limited and includes only ten full-papers. Two phase I [52,53], and four phase II studies [54-57] are prospective. The remaining four series are retrospective [44,58-60]. All the studies are mono-institutional and include mainly GBM patients. Overall, 287 patients were treated between 1996 and 2008: 249 (87%) with histologically confirmed GBM, and 38 (13%) with proved grade III gliomas.

The main features of these series are reported in Table 2.

The patients were treated over a long time period with a consequent wide variability concerning the use of both RT (dose per fraction and total dose) and CHT (type of drug, schedule and administration timing). Unfortunately, such variations make difficult to accept or reject, at the first analysis, the thesis that a certain difference in outcomes (if any) is only IMRT-related. Therefore, considering that treatment parameters can influence the clinical outcome, the relevance of each treatment component has to be deeply analyzed. Thereafter, each study has not to be compared with the present standard of care only, but a comprehensive comparative analysis with similar non-IMRT clinical series is mandatory. In fact, the clinical advantage coming from the use of IMRT could not emerge in comparison with the current standard of care because of the inferiority of a CHT schedule non-TMZ based. Conversely, such a gain could be revealed in comparison with series employing similar CHT regimens. Moreover, for the same CHT, the outcome improvement could come from the difference in the radiation regimen. Regarding CHT, a meta-analysis of studies using mainly nitrosoureas (NU) [19] and a randomized phase III study with the use of TMZ [4,61] are available so that they seem the natural element of comparison. However, also reference studies dealing with hypofractionation in HGG patients have to be considered. With this regard, as mentioned in the “potential” section, most studies reported in the literature mainly deals with “poor prognosis” patients. Considering that also the patients’ characteristics play a prognostic role it is proper to evaluate these features. Overall, the patients belong to a relatively good-prognosis population. However, it is to note that in some series prognostic factors, such as performance status, recursive partitioning analysis and extent of surgery, differ from the general trend or were not specified (see Table 2). Therefore, only reference studies dealing with hypofractionation in HGG patients with good prognosis are a useful element of comparison. With this regard, the number of series delivering hypofractionation in this sub-set of patient is very limited and based on phase I-II studies [62-64].

The main features and results of the reference studies are reported in Table 3.

Finally, regarding the radiation regimens it is to note as the wide range of dose per fraction and total doses delivered could be misleading because it is difficult to quantify the influence of the absolute dose. Therefore, only the analysis of the corresponding BEDs can allow a proper comparison with respect to reference regimens. However, as aforementioned, the issue concerning the α/β ratio of HGG has several uncertainties. Nevertheless, assuming an α/β ratio of 10 Gy, an effective doubling time of 5 days, and a kickoff time for accelerated repopulation of 14 days, seems a reasonable way to properly simulate the HGG biological behavior (data reported in Table 2). This analysis confirms the scattering of prescribed doses but also shows that only three studies [53,56,57] achieved a relevant increase both of the dose delivered to gross tumor volume (GTV) and of the BED.

Analyzing the data in such terms seems possible to split the studies into 4 sub-groups ultimately making easier the outcome interpretation.

Two authors [44,58] delivered a conventional radiation regimen with a total dose of 59.4-60 Gy and a dose per fraction of 1.8-2 Gy. In Fuller et al. [58] CHT was mostly based on a mono-chemotherapy with NU (lomustine or carmustine), irinotecan, penicillamine or TMZ while Narayana et al. [44] did not report details regarding the drugs and scheme used. Considering the period of treatment (2001-2003) seems logical to assume a scheme mostly based on NU. With an overall median OS and PFS of 9 [44] and 7.3 [58] months respectively, primary endpoints do not show any improvement regardless of the element of comparison. Conversely, treatment related acute toxicity rate is lower with respect to the current standard of care. In summary, harnessing IMRT to deliver a conventional treatment can improve the patient compliance.

In two series [54,55] IMRT was delivered according to a hypofractionated regimen (3-5 Gy/fraction) but without neither a significant dose escalation nor the administration of CHT. The analysis of BEDs shows values almost equivalent to the standard regimen and higher than reference hypofractionated schedules. Overall, these studies achieved a median OS and PFS of 9.5 [54] and 6 [55] months, respectively. As expected, there was a higher risk of late neurotoxicity. Concerning primary endpoints, these results are consistent with both standard and hypofractionated historical series. However, they are even worst in terms of sequelae (expecially radionecrosis). The outcomes are however inferior to the current standard probably due to the lack of CHT administration. In summary, the delivery of a hypofractionated treatment BED-equivalent to the standard regimen and without any CHT did not seem to produce any improvement.

Three authors [53,56,57] reported the use of hypofractionation (2.5-8.5 Gy/fraction) along with a significant dose escalation. As stated above, it is worth of note as such series achieved a relevant increase both of the dose delivered to GTV and of the BED. Monjazeb et al. [53] did not administered CHT, while Nakamatsu et al. [57] employed a multi-drug combination of lomustine, vincristine and interferon α. Iuchi et al. [56] did not report any detail concerning the employed scheme of CHT. Again, considering the period of treatment (2002-2004) seems logical to assume a scheme mostly based on NU. Only the study with highest BEDs (in association with CHT) demonstrates the possibility to improve primary outcomes [56] regardless of the element of comparison. However, the phase I protocol of Monjazeb et al. [53] aimed to report the treatment tolerability/toxicity and was not powered to detect a survival advantage. Conversely, all the three studies support the feasibility of such

regimens: acute side effects are equivalent or slightly inferior to those registered with conventional treatment though emerges the concern regarding cerebral necrosis.

In the remaining studies [52,59,60] IMRT was delivered with slightly hypofractionated schemes (2.4-3 Gy/fraction) and without a significant total dose increase. The maximal corresponding BEDs ranged between 74 and 82 Gy. However, most patients included in these studies received the standard schedule of TMZ. In this sub-group of studies, 2 out of 3 series demonstrated the possibility to improve primary outcomes [52,60] regardless of the element of comparison, while all of them proved the feasibility of such regimens. However, it is proper to remark that the study of Morganti et al. [52] was not designed to detect a survival improvement, and the data of Cho et al. [60] were retrospectively analyzed. Therefore, these results have to be confirmed in future prospective trials. In summary, the improvement in OS and PFS seems achievable by hypofractionation with a BED equivalent to or slightly higher than conventional regimen in association with the standard schedule of TMZ. Toxicity appears to be similar and without the concern of radionecrosis, while the overall treatment time is shortened.

The last consideration regards the pattern of failure. The site of recurrence is available for 163 patients: 137 of them (84%) failed centrally and 26 outside the location of the primary tumor (i.e. distant more than two cm). These data clearly show that the majority of cases continued to recur in the immediate proximity of the primary tumor. Nevertheless, when an extremely hypofractionated regimen and a more sophisticated target assessment were adopted [56], an excellent local control rate was achieved. This study also pointed out that cerebrospinal fluid dissemination was the most frequent failure pattern. These data suggest the possibility to achieve the control of the infiltrating cells closer to the primary tumor providing more time to recur outside of radiation target.

Despite the usefulness of the present analysis, some features of the considered studies deserve further remarks and can potentially weaken the previous considerations. All published series are mono-institutional with no control group. The reported sample size of the studies is often quite limited with a range of 13–58 patients (mean, 29). Fifty seven percent of patients [44,58-60] were retrospectively analyzed.

No CHT was administered in 23% of cases [53-55] and only 24% of patients [52,59,60] received TMZ (it is well known that before the introduction of TMZ in the treatment of GBM, the addition of CHT to radiotherapy had been a controversial issue [19]).

All studies enrolled mainly GBM patients whereas only 38 AAs received IMRT.

The target definition was always based on conventional imaging, but varied widely among studies (see Table 2). Although discrepancies in target volume definition do not seem to alter the central pattern of failure of GBM, the volume of irradiated healthy brain can change considerably [18,65], ultimately affecting neurotoxicity.

In summary, we can highlight the following:

- Only a limited number of clinical studies reported in the literature evaluated the role of IMRT in the treatment of HGG.
- Overall, the features diverge from series to series, and only a deep sub-group analysis can detect the areas of outcomes improvement.

- The "overall quality" of the studies supports a grade II-III scientific evidence (there are only small, prospective or retrospective series).
- Such evidence mainly regards GBMs, while no conclusions can be drawn concerning AAs.

In order to strengthen the evidence and test new areas of improvement, the application of IMRT in HGG deserves further evaluations in properly designed prospective trials.

Perspectives

Potential Impact of Plan Comparison Studies on the Clinical Practice

The results of the planning comparisons are very consistent among the studies available in the literature and can be summarized as follows:

- In simple cases, 3D-CRT and IMRT techniques provide similar target coverage;
- As a consequence of a slightly superior dose homogeneity and a (largely) superior dose conformity, IMRT is somewhat better than 3D-CRT in reducing the maximum dose to the organs at risk, although to an extent that varies considerably from case to case;
- IMRT is clearly better than 3D-CRT at sparing the healthy brain at medium to low doses;
- There is no aspect in which IMRT seems to be worse than 3D-CRT, with one possible exception (results reported only by Piroth et al. [41] concerning dose to the healthy brain in medium-low dose region);
- All IMRT techniques (i.e. static and rotating) have a very similar quality of the dose distribution, i.e. the transition from static-field IMRT to Tomotherapy or VMAT is not likely to bring dramatic improvements.

As a consequence, we think it's possible to draw the following considerations concerning the clinical use of IMRT in HGG:

8. From a purely dosimetric standpoint, there is no reason to not apply IMRT. In fact, the strongest criticism towards the IMRT dose distributions is often that the increased conformity comes at the cost of an increased 'dose bath'. All but one [41] studies reported in literature suggest that such problem does not apply to the treatment of gliomas. It is true that the clinical significance of the dosimetric benefits allowed by IMRT has not been proven in clinical trials and that it should therefore be systematically quantified, nevertheless such dosimetric benefit exists.
9. The large-scale implementation of IMRT is often made difficult by logistical/organisational difficulties, e.g. increased time for planning or verification [66]. As a consequence, a practical approach may consist in selecting those patients

most likely to benefit from IMRT. The planning studies we analyzed from the literature showed (very) similar dose distributions in the target volumes and a large variation of sparing allowed by IMRT in the OARs. This may be a quantitative confirmation of the idea that HGG patients present very different situations in terms of target volume size, shape and proximity to OARs. Therefore, we think it's interesting to assess whether few well defined selection criteria can be found in HGG, which could single out those cases likely to get the most out of IMRT. In this sense, our preliminary results [51] already suggest that when more than two OARs overlap with target volume, IMRT allows for a better target coverage while maintaining an equivalent or better OARs sparing. These findings could be the basis to recommend the way to identify a selection protocol aimed to drive toward the most suitable choice in HGG patient management.

10. All but one [41] studies reported in literature showed that IMRT is associated with a decrease of both the healthy brain dose and, in general, of the mean OARs doses. There are no data suggesting to what extent this dosimetric benefit will translate into a clinical advantage. At the same time, OARs such as brainstem, chiasm, optical nerves etc., may suffer complications that significantly decrease the quality of life, thus justifying a very conservative approach where strictly defined dose tolerances are enforced. As a consequence, IMRT treatment planning should probably attempt to achieve decreased healthy brain irradiation only when this treatment objective does not affect other dosimetric parameters more strictly associated to the patient clinical outcome and quality of life in the short term.

Clinical Standpoint

The previous sections clearly point out that the great potential of IMRT has been exploited to test several hypotheses. Probably most of them would deserve a large-scale clinical implementation and/or further evaluations. However, such a step seems difficult to be achieved and the best approach could be to concentrate one's efforts into few, well defined areas.

From this standpoint, three questions could make easier such a task:

- Can we further increase the accuracy of the treatment planning? In case, how does it interact with IMRT delivery?
- Did IMRT studies suggest any promising radiation regimen worthy of further investigation?
- What kind of patients should we include?

With regard to the first issue, it is proper to highlight that in HGG both for 3D-CRT and IMRT the targets definition is based on conventional imaging so far. However, conventional CT and MR imaging does not reliably indicate nor the true extent of gliomas nor the aggressiveness of different tumor components. Therefore, different imaging modalities, such

as functional MRI, MR spectroscopy and diffusion tensor imaging (DTI) as well as PET scans have been used to visualize the clinically relevant volumes.

Early studies have shown the feasibility of incorporating functional and spectroscopic MR images [67] as well as DTI [68] into treatment planning. At the same time, it did result in a significant change in target location, volume and shape compared to conventional MR imaging suggesting the possibility to deposit different dose levels to different targets. Such approach could translate into a better tumor control and healthy tissue sparing [67,68]. By the means of amino acid PET, Grosu et al. [69] pointed out similar conclusions highlighting a very high sensitivity and accuracy of such modality. Even though the evidence is not robust yet, it is reasonable to consider their routine application not far to be achieved.

On the one hand, such considerations suggest that both 3D-CRT and IMRT could benefit from new imaging techniques. On the other hand, in presence of several sub-targets to be treated at different dose levels, one could expect that 3D-CRT encounters more difficulties to comply with dose constraints whereas IMRT can maximally exploit its own potential as observed in head and neck tumors [70]. Therefore, considering the IMRT studies on HGG, it could be that target definition based only on morphological imaging probably did not permit to take full advantage of the dose delivery capability of IMRT.

In summary, the new imaging modalities can improve the assessment of tumor extent ultimately increasing the complexity of target definition and dose prescription. In this scenario the advantage of IMRT over 3D-CRT could further increase making IMRT the gold standard to manage such situations.

Concerning the second question, some brief considerations can easily suggest the proper answer.

The employment of IMRT to deliver a conventional radiation regimen along with standard of care CHT can translate only into a better patient compliance without any improvement in primary endpoints.

The concern regarding the proved risk of late neurocognitive effects in long-term survivors [25] together with the proved higher rate of radionecrosis [55,56] hinder further evaluations about the use of hypofractionated schemes with a high dose per fraction. Actually, such a strategy demonstrated the possibility to improve both OS and PFS [56], but side effects could be unaccettable.

Conversely, the safety and feasibility of slightly hypofractionated radiation regimens delivered by SIB IMRT in association with standard of care CHT have been already demonstrated [52]. Therefore, considering its striking potential (dose-painting, hypofractionation along with dose-escalation, overall treatment time reduction) such a strategy seems the best approach to achieve the improvement of primary endpoints keeping toxicities at least at the same level. This hypothesis should be verified by a properly designed prospective trial.

Finally, in order to optimize the efforts, it could be useful to assess whether a particular sub-group of patients will benefit most from the aforementioned newer approaches.

So far, the RTOG RPA classification [6] represents the most reliable model to predict survival among homogenous subsets of HGG patients according to their treatment and pre-treatment variables. As such, it is widely used as decisional criterion to single out the most proper treatment strategy according to the patient features. Usually, patients that fit with

classes I to IV have the longest life expectancy and are suitable for a maximal treatment (surgery followed by RT and CHT). Conversely, patients that belong to classes V and VI have a poor prognosis. Therefore, aim of the treatment is to improve the symptoms due to tumor growth while preserving the QoL. The optimal management of such patients has not been determined yet, and the treatment can include supportive care only, a short course of RT and/or palliative CHT.

In this framework, IMRT can represent a useful tool to improve the therapeutic ratio in both strategies. In poor prognosis patients, where treatment volumes are often very huge, its capability of healthy structure sparing can reduce the early radiation related side effects keeping as long as possible an adequate QoL. In good prognosis patients, as stated above, the use of IMRT raises reasonable expectations of survival improvement even though the proof of a true advantage in comparison to the standard 3D technique can be demonstrated only with properly addressed prospective-comparative studies [71].

Conclusion

IMRT represents an evolutionary advance in radiotherapy practice. The limited data currently available on HGG suggest that we still should wonder *whether, or to what extent,* the dosimetrical superiority of IMRT translates into a clinically relevant advantage over 3D-CRT. However, considering the variability of HGG in terms of tumor location and patient clinical conditions the proper question could be about *in which clinical scenario* one can get the best advantage from IMRT application. This approach seems the best method to definitively quantify such a benefit.

Conflict of Interest Statement

The authors have no conflicts of interest.

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