Three-Dimensional Conformal Radiotherapy in Treatment of High Grade Glioma

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Conflict of interest: None declared.

Funding: No funding sources

Abstract

3-D conformal radiotherapy (3-D CRT) is the term used to describe the design and delivery of radiotherapy treatment plans based on 3-D image data with treatment fields individually shaped to treat only the target tissue. The European Dynarad consortium has proposed that the complexity of radiotherapy planning and treatment methodologies can be captured in four levels. Level 0 represents basic radiotherapy where no attempt is made to shape the treatment fields and as such cannot be described as conformal. This level will not be considered further in the current publication. Conformal radiotherapy permits the delivery of a radical dose of radiotherapy while limiting the dose to normal tissue structures, thus minimising the adverse effects of treatment. Its principle benefit therefore is to patients who are to be given potentially curative radiotherapy. Where radiotherapy is being given with palliative intent the prescribed total doses are usually lower and the adverse effects of palliative radiotherapy are therefore likely to be less. For this reason conformal radiotherapy is not often used when delivering palliative treatment, although it is always desirable to minimise the volume of non target tissue that is irradiated. Conformal radiotherapy can be regarded as a step towards intensity modulated radiotherapy (IMRT). However, the delivery of IMRT, where fields are made up of multiple beamlets, is considerably more costly than conformal radiotherapy and requires an even higher level of expertise. There is considerable evidence for the benefits of 3-D CRT, but the benefits of IMRT are less well established. The incremental benefits in the transition from conventional radiotherapy to 3-D CRT are therefore substantially greater than those achieved in the transition from 3-D CRT to IMRT. It is therefore recommended that the implementation of 3-D CRT should be given priority over the implementation of IMRT

Keywords: Three-dimensional, conformal radiotherapy, High Grade Glioma

TobRegul Sci. ™ 2023; 9(1): 8347 - 8363

DOI: doi.org/10.18001 /TRS.9.1.589

Introduction

3-D conformal radiotherapy (3-D CRT) is the term used to describe the design and delivery of radiotherapy treatment plans based on 3-D image data with treatment fields individually shaped to treat only the target tissue. The European Dynarad consortium has proposed that the complexity of radiotherapy planning and treatment methodologies can be captured in four levels. Level 0 represents basic radiotherapy where no attempt is made to shape the treatment fields and as such cannot be described as conformal. This level will not be considered further in the current publication [1]. Individually shaped fields can be designed from planar radiographs or with limited computer tomography (CT) data. This level of conformal radiotherapy (Table 3) can be carried out in any radiotherapy department with the minimal facilities and is a useful way to begin the move towards full 3-D CRT. Level 2 conformal radiotherapy requires a full 3-D data set, usually of CT images, on which the tumour volume is defined following the concepts of ICRU 50 and 62. This level may include the use of non-coplanar beams. Level 3 represents the most complex radiotherapy treatments, including IMRT, many of which are still at the research stage in University Hospitals [2].

Table 3 is intended to give a flavour of the progression of techniques that may be available at each level and should not be regarded as a prescriptive indication that every treatment should use all the techniques listed.

	Level 1 Basic CRT	**Level 2 3-D CRT**	**Level 3 Advanced 3-D CRT**
1. Patient data acquisition			
Immobilization	Desirable	Customized to the patient	Customized to the patient
Imaging system	Localization film, few CT slices optional	Thin slice CT slices, MR optional	Registered CT with MR or PET
Anatomical data	Height above couch and skin marks	External markers or frame	Implanted markers or frame
Reference marks for setup	Contour individual slices	3-D segmentation	3-D segmentation
Critical organs			
Inhomogeneities	Optional	Contours every slice or vessel based	Vessel based correction
Gross tumour volume (GTV)	May not be formally defined	Contours every slice	3-D segmentation
Clinical target volume (CTV)	May not be formally defined	Grown from GTV using auto-margin	Margin growing from GTV + individualized 4-

		growing Based on standard	D CT data or other TV
Internal target volume (ITV)	May not be formally defined	Based on standard values	
2. Beam definition			
Accounting for beam setting uncertainty	Margins are not customized	3-D margins based on audit of setup errors	Image guidance
Type of radiation and beam modifiers	Photons or electrons No wedges	Photons, wedges, field shaping	Photons + IMRT
Beam incidence	Coplanar beams	Several (including non-coplanar) beams	Multiple non-coplanar beams or arcs
Isocentric	SSD or SAD technique	SAD technique (auto setup of table)	SAD technique (auto setup of table)
Beam limiting device	Non-customized shielding blocks	Individual MLC or customized blocks	MLC or mini MLC
PTV - CTV margin	Shape drawn on simulation films	Proposal margins based on audit	Individual margin based on e.g. 4-D CT
3. Dose calculation and optimization			
Calculation algorithm	1-D or 2-D tissue inhomogeneity	2-D or 3-D with inhomogeneity	3-D or 4-D with inhomogeneity
Evaluation of treatment plans	Isodoses on central slice or several slices	Isodoses viewed in 3-D on computer with DVH	3-D isodose surface + DVH, TCP, NTCP
Treatment plan optimization	Non-computerized	Simple computer optimization	Inverse planning
4. Treatment verification and execution			
Verification simulation	Normal practice	Useful	Replaced by IGRT on treatment machine
Immobilization	Desirable	Customized to the patient	Individual cast or stereotactic frame
Aids for positioning	Laser + light field	Isocentric lasers	Lasers or frameless stereotaxy

Patient positioning	Height above couch + skin marks	Move from anatomical reference or stereotaxy	Daily image guidance
Verification of patient setup	Light field	Port films	CT data compared to reference CT
Record and verify system	Desirable	Essential but network is optional	Essential including TLD or diodes or EPID
In vivo measurements	Desirable	TLD or diodes	transit dosimetry

Conformal radiotherapy permits the delivery of a radical dose of radiotherapy while limiting the dose to normal tissue structures, thus minimising the adverse effects of treatment. Its principle benefit therefore is to patients who are to be given potentially curative radiotherapy. Where radiotherapy is being given with palliative intent the prescribed total doses are usually lower and the adverse effects of palliative radiotherapy are therefore likely to be less. For this reason conformal radiotherapy is not often used when delivering palliative treatment, although it is always desirable to minimise the volume of non target tissue that is irradiated [3].

Conformal radiotherapy can be regarded as a step towards intensity modulated radiotherapy (IMRT). However, the delivery of IMRT, where fields are made up of multiple beamlets, is considerably more costly than conformal radiotherapy and requires an even higher level of expertise. There is considerable evidence for the benefits of 3-D CRT, but the benefits of IMRT are less well established. The incremental benefits in the transition from conventional radiotherapy to 3-D CRT are therefore substantially greater than those achieved in the transition from 3-D CRT to IMRT. It is therefore recommended that the implementation of 3-D CRT should be given priority over the implementation of IMRT [4].

The design and delivery of a 3-D CRT treatment requires a chain of procedures all of which must be in place if the treatment is to be safe and accurate. A chain is as strong as its weakest link. If any of the links of a chain are weaker than the others the chain will break at that point, which illustrates the need for all the components of the conformal therapy programme to be in place. It is therefore essential that all the links have been established before embarking on patient treatment. The links in this chain are [3]:

- the precise immobilization of patients throughout the whole process;
- the use of high quality 3-D medical imaging to determine the gross tumour volume (GTV), clinical target volume (CTV), planning target volume (PTV) and planning organ at risk volume (PRV);
- the use of 3-D planning systems to choose beam orientations and to display beam’s-eye-views (BEVs);
- the planning of beams;
- the computation of 3-D dose to the PTV and PRV;

- the evaluation of the dose plan and the biological effect using dose volume histograms (DVH), tumour control probability (TCP), normal tissue complication probability (NTCP);
- the transfer of these planning data to the delivery machine;
- the verification of patient position, beam placement and dosimetry;
- the measurement of outcome.

Clinical evidence for 3-D conformal radiotherapy

The ideas of three-dimensionality, beam shaping, and irradiation of tumours through multiple fields from different beam angles to reduce the dose to normal tissues have always been present in radiotherapy practice. When the appropriate technology to deliver 3-D CRT, such as CT simulators, radiation treatment planning systems (RTPS) capable of performing three dimensional dose calculations, producing digitally reconstructed radiographs (DRRs) and DVHs, and beam shaping devices such as multi-leaf collimators (MLCs) became available, this way of planning and delivering radiotherapy soon gained popularity. This has now become standard practice in the developed world when treating many types of tumours with curative intent [5].

The aims of 3-D CRT are to achieve conformity of the high dose region to the target volume and consequently to reduce the dose to the surrounding normal tissues. This should reduce both acute and late morbidity. If the adverse effects of treatment can be reduced in this way, the dose to the target volume can be increased with the expectation of improved cure of the tumour [6].

The largest body of available evidence in support of 3-D CRT is in the treatment of prostate and lung cancers. By conforming the dose to the target volume, a reduction in the treated volume of about 30% to 50% can be achieved using 3-D CRT, and this reduction includes only normal tissues. Local control can therefore be improved by increasing the dose delivered to the tumour, without unacceptable toxicity. Evidence exists of a dose-response relationship in many tumours. This possibility of escalating doses, thus increasing local control and potentially improving survival, can help to change the treatment approach in many tumours from palliative to potentially curative [7].

3-D CRT with dose escalation has been used to study the possible improvement in tumour control in a number of Phase II [8,9] and randomised studies [10] in prostate cancer. [11] demonstrated that doses over 74 Gy improve local control in prostate cancer and [12] reached the same conclusion in a randomized trial. In a randomised study of 3-D CRT against conventional radiotherapy, Dearnaley et al. demonstrated a significantly lower risk of developing late radiation-induced proctitis in the patients treated in the 3-D CRT arm. Their subsequent RT01 randomised trial showed improved biochemical prostate specific antigen (PSA) control with dose escalation of 74 Gy versus 64 Gy, using 3-D CRT [13].

A systematic review of 3-D CRT for prostate cancer was carried out by American Society of Therapeutic Radiology and Oncology (ASTRO) and the paper by Morris et al. summarized the results. Seventy two published articles were included. It was found that gastrointestinal and genitourinary toxicities were lower in patients treated with 3-D CRT than with earlier techniques [14].

[15] published another systematic review of radiotherapy in prostate cancer, including randomized trials, prospective trials, and 210 retrospective studies, with a total of 152 614

patients. The conclusions were that dose escalation could be safely performed with 3-D CRT, and that its use resulted in reduced late rectal toxicity and acute anal toxicity compared with radiotherapy administered with non-conformal treatment volumes.

A third systematic review on prostate cancer, published by Brundage et al. showed that the use of 3-D CRT reduces the rates of both early and late bowel and bladder toxicity, and that escalation of the dose results in increased biochemical response and control rates [16].

A number of Phase I studies have demonstrated the tolerability and feasibility of dose escalation with 3-D CRT in lung cancer. Bradley reviewed the dose escalation RTOG lung trials and reported that doses can be escalated using 3-D CRT from 60 Gy (RTOG 9410) to 83.8 Gy (RTOG 9311). When 3-D CRT is combined with chemotherapy, the maximum tolerable dose is in the range of 70 Gy to 74 Gy. The initial cost of implementing 3-D CRT is greater when compared with the implementation of a conventional 2-D programme. On the other hand, the replacement of custom blocks by an MLC can save between 5% and 20% of treatment time. Some cost analyses have demonstrated that the initial bigger implementation cost is counterbalanced by the improvement in treatment outcome, resulting in lower overall costs of care [17].

Imaging equipment

All radiation therapy centres require diagnostic imaging equipment for optimum imaging of each tumour site. Ideally, each cancer centre will have a CT simulator housed in the radiation therapy department. If this is not possible, radiotherapy departments must have access to a CT scanner for planning conformal radiotherapy. Other imaging modalities that are useful (but not essential) in the delineation of target volume are magnetic resonance imaging (MRI), ultrasound (US), and various functional imaging modalities such as positron emission tomography (PET), single photon emission computer tomography (SPECT), functional MRI, MR spectroscopic imaging, and molecular imaging. The rationale for use of 3-D image information is to improve the accuracy with which both the target to be irradiated, and the organs at risk to be spared, may be defined. The incorporation of information from multiple imaging modalities has proven useful in this regard, but again is not an essential prerequisite [18].

For this purpose it is useful to be able to co-register the data from other imaging modalities with the planning CT data. In the case of PET images this can be difficult because of the need to identify common structures and the relatively poor resolution of PET images. For this reason PET scanners are often combined with CT scanners (PET/CT) so that the frames of reference of the PET and CT scans are identical and the images are automatically in registration with each other [19].

Immobilization

Because of the nature of conformal radiation therapy treatment, reproducible immobilization techniques are essential to safely use this treatment technique. Examples include thermoplastic masks with bite block fixation, alpha cradle etc. However, it is not necessary that such positioning systems are used for every treatment. Techniques to reduce or follow internal organ motion, such as by using ultrasound localization of the prostate or respiratory gating, may be desirable in some applications. All these procedures will impose their own costs with respect to procedure design, training, and validation. If not already known, it will be necessary to study the reproducibility that can be achieved with the immobilization system in order to establish realistic margins for treatment planning [20].

3-D radiation treatment planning systems

All centres should have a 3-D RTPS that must have a number of particular features for satisfactory planning of conformal radiotherapy. These will include features pertaining to data acquisition, dose calculation and information display.

Treatment machine

A linear accelerator fitted with a MLC is ideal for the delivery of planned conformal radiation therapy. Ideally, the accelerator will also be fitted with an electronic portal imaging device (EPID) that can be used for the verification of patient setup and geometric verification of beam portals. If an accelerator is not fitted with an EPID, conventional port films can be used for the verification of patient setup and beam portals. Additionally, if MLCs are not available, conformal radiation therapy can be delivered by making use of low-melting-point-alloy blocks. Successful 3-D CRT can also be achieved with a cobalt-60 unit using low-melting-point-alloy blocks (and it is also possible to do IMRT using solid compensators) [21].

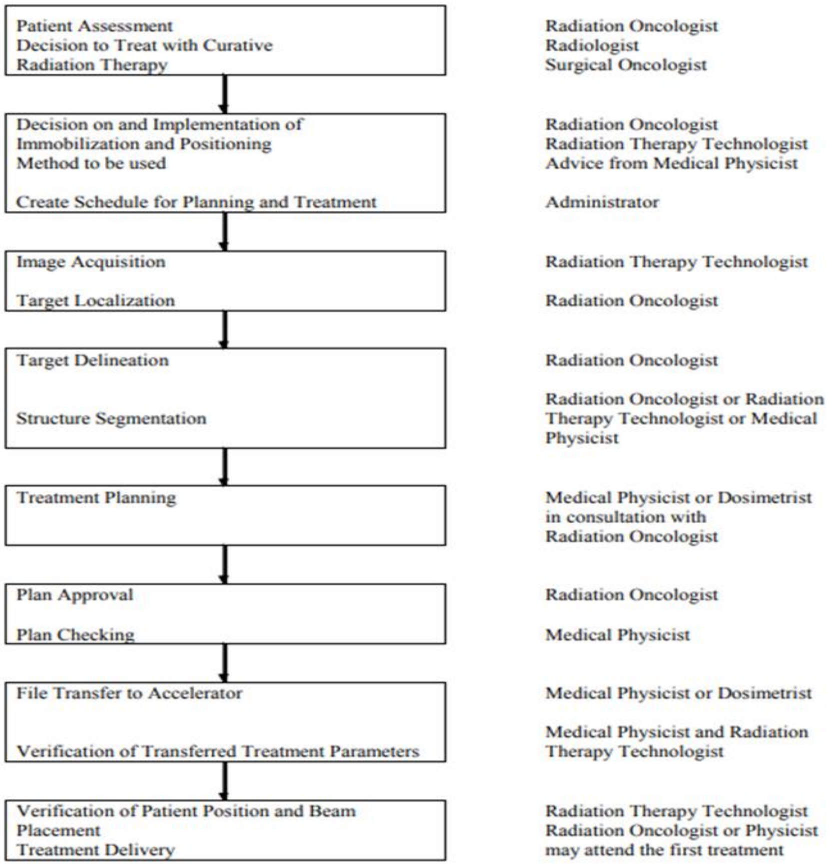
Record and verification system and networking

When a MLC is used, a record and verification (R&V) system is needed to ensure, as a minimum, that the planned conformal radiation therapy is delivered as per prescription. Care must be taken to ensure that errors do not occur during transfer of data between treatment planning systems, simulator and treatment machine. An electronic network system for data transfer from imaging facilities to the RTPS and then to the delivery systems is desirable and this should comply with DICOM (Digital Imaging and Communications in Medicine) DICOM-RT protocols. If networking capabilities are not available, then an alternative means of data transfer, such as the use of CD-ROM, should be developed to ensure accurate transfer of digital data from scanning facilities to RTPS and from the RTPS to the delivery systems [22].

Clinical Implementation Of 3-D Conformal Radiotherapy

The treatment team should work through the questionnaire before treating their first patient using 3-D CRT.

Figure 1 shows a flow chart of a typical 3-D CRT process. Details of this process may vary from one institution to another. However, this figure serves as an illustration to understand and discuss the various steps in the clinical implementation of 3-D CRT in a typical clinic [3].



Patient assessment and decision to treat with radiation

The first step in the process is patient assessment and deciding how the patient should be treated. During assessment various diagnostic and investigative procedures are undertaken to define the state of the disease. This involves imaging, biochemical testing and review of pathologic information to identify the type, stage and grade of the cancer. The decision to treat the patient with radiation should be made by a team of clinicians [23].

Immobilization and patient positioning

Before starting to develop the treatment plan the team needs to decide on the position required for the patient treatment and on any immobilization aids that are to be used. The use of 3-D CRT is usually associated with a reduction in the margins around the CTV, but this is only safe if random and systematic errors can be reduced. Effective immobilization can significantly reduce setup errors. Therefore design of a given immobilization system for accuracy, comfort and ease of use is an important factor affecting the precision of patient set up on the treatment machine during the entire course of treatment delivery. Each centre should evaluate the immobilization system used for a given site for accuracy of reproducibility of patient positioning [24].

An accurately set up laser alignment system is an essential requirement for accurate radiotherapy. This should consist of at least three lasers to provide two lateral crosses and a sagittal line which can be used in conjunction with appropriately placed tattoos to ensure the patient is not rotated. Special immobilization systems are available for immobilizing different parts of the body. For example, knee supports and ankle stocks are used for pelvic and abdominal immobilization, adjustable breast boards are used for breast and vacuum immobilization bags or alpha cradles are used for chest, thermoplastic masks are used for head and neck treatment, and relocatable stereotactic frames are used for brain tumours. The key to satisfactory positioning of the patient is to ensure that they are as comfortable and relaxed as possible. It is often more practical and accurate to have minimal immobilization aids accurately placed by a skilled team of RTTs, than an over-complex system [25].

Image acquisition and target Localization

Every radiotherapy department should develop protocols for image acquisition for various body sites. These protocols will define the requirements for the most common treatment sites. Where a protocol is not available, or in cases where it needs to be modified, a discussion with regard to the goals of the treatment should take place between the treating radiation oncologist, medical physicist, dosimetrist and CT technologist. This is necessary so that a clear understanding of the planning needs is well established prior to image acquisition [26].

Segmentation of structures

3D-CRT treatment planning is based on an image based simulation approach for accurately delineating tumour and organs at risk volumes for an individual patient. These volumes are drawn on a slice-by-slice basis on a CT data set. Target volumes are contoured manually although modern treatment planning systems provide capabilities to segment various structures automatically. It is incumbent upon the radiation oncologist to ensure that target volumes drawn by him/her or via the automatic segmentation process are accurate. This places a premium demand on the radiation oncologist to specify targets with greater precision and on the medical physicist to develop procedures for accurate imaging, patient setup reproducibility and organ motion assessment and treatment delivery verification. The following provides guidelines for delineation of target volumes and organs at risk volumes [27].

Treatment planning for 3-D conformal radiotherapy

The treatment planning process

Once the target volume, organs at risk, and the required doses have been defined, the treatment plan will be produced by a person trained in 3-D planning. The aim of the treatment planning process is to achieve the dose objectives to the target and critical structures and to produce a dose distribution that is “optimal”. The radiation treatment planning systems have the capability to display a three dimensional view of the virtual patient on the computer monitor with contoured structures and target volumes utilizing various renderings, colours and degrees of transparency. The beam angles can be chosen using standard templates such as a six field prostate plan or by using a beam’s-eye-view display to maximize PTV coverage and to minimize irradiation of critical structures [28].

When a beam aperture is defined, an additional margin of about 7 to 8 mm needs to be added beyond the PTV in all directions in the transverse plane to obtain the desired dose coverage to the PTV. In the superior inferior directions one needs to add about 12 to 15 mm margin because of beam divergence effects. These margins are needed to cover the PTV with a minimum isodoses line or surface. A number of iterations are often required and, unless the radiation oncologist is actually doing the plan, there may need to be discussions between the radiation oncologist and the planners when dose objectives conflict. For conformal radiotherapy it is recommended that the radiation dose should be reported according to ICRU Reports 50 and 62 [29,30], for the purpose of correlating dose with clinical outcome [31].

In most cases, the dose prescription will specify the dose using the same ICRU criteria as those for reporting, i.e. the dose is specified at the ICRU reference point at or near the centre of the PTV, stating the maximum and minimum doses over the 3-D target volume as well as the mean dose. Specification of doses used for both prescription and reporting of IMRT is difficult where non-uniform dose distributions present new problems. Modal doses (i.e. the most frequently occurring dose value) within target volumes may in some cases be lower than for current treatment techniques and this may influence the choice of prescription doses. It is likely that entire DVHs for each volume (PTV, CTV and PRV) will need to be reported to allow correlation with clinical outcome [32].

In its most basic implementation conformal radiotherapy may consist of coplanar static beams in a standard geometric configuration with MLCs or conformal blocks used to achieve the required conformal shape. Non-coplanar planning increases complexity and raises questions not encountered in traditional coplanar planning, e.g. beams may enter and exit through different anatomical structures. This may affect acute or late responses and non-coplanar beam arrangements should be used with caution. However, for brain treatments a shaped non-coplanar beam may be very useful to create a concave volume normally only achievable by IMRT [33].

Sufficient information must be provided to ensure precise treatment prescription, set up and delivery. For non-standard configurations of beams, DVHs may aid in the selection of the best plan, but it is important to note that DVHs contain no geometric information, i.e. they do not indicate which part of the organ is receiving a high or low dose. Clinical plan comparison should therefore involve inspecting DVHs and physical dose distributions (slice by slice or using volume rendered images) at the treatment planning terminal [34].

Additionally, biological modelling with computation of tumour control probability (TCP) and normal tissue complication probability (NTCP) may be valuable, but such modelling is complex and can be very sensitive to the choice of values for various parameters. Where complex computer calculations are to be used (e.g. non-coplanar beams, asymmetric beams or 3-D-algorithms), it is particularly important to have expert input from an experienced radiotherapy physicist. This should typically include specification of beam set-up parameters, isodose plots on one or more sections, DVHs, and BEVs with or without DRRs [35].

Radiation treatment planning system requirements

The treatment planning system must have a number of features for planning of conformal radiotherapy. These can be divided into geometric and dose computational features.

Geometric features

The planning system must be able to handle a large data volume set which may include as many as 120 CT slices. A narrow slice spacing (≈ 3 mm) is necessary to produce satisfactory DRRs but this may make dose calculation rather slow. It is therefore advisable, if it is possible, to select a subset of slices for contouring and the dose calculation. Systems for 3-D visualisation of anatomy, of the outlined structures and of the dose overlay are essential. Co-registration of images from different modalities is a useful feature that becomes essential for some sites.

Systems for design of treatment aids (e.g. shielding blocks, compensators, etc.) and visualizing the position of the radiation beam in 3- D are also useful. [3]

Dose computation models

The combination of beams from many directions, especially if these are non-coplanar, means that purely geometrical considerations are no longer adequate to determine the position of MLC leaves. It is therefore important that the computer has a fully 3-D dose computation model that will permit accurate calculation of the dose both at the centre of the volume and at the position of isodose lines close to the edges of the beams. When multiple beams are in use, the calculation of the doses at points that are geometrically shielded by the collimation system may become significant. Accurate modelling of all the components of the linear accelerator collimation system is important, especially in terms of the attenuation of the leaves and leaf ends of the MLC and the combination of the leaves with the jaws [36].

Number of planning workstations

While the number of workstations required depends on the organisation of the department, it is essential that there are a sufficient number of workstations so that staff are not having to carry out 3-D treatment plans under time pressure. With increasing use of CT data associated with 3-D CRT, the requirement for workstations is likely to increase. A minimum number is one workstation per megavoltage treatment machine, but two per treatment machine is recommended [37].

Dose calculation and treatment plan optimization

CT acquisition, 3D reconstruction and the BEV tool are used to generate the treatment plan. The use of BEV permits the best choice of gantry and collimator rotation and the optimal definition of shape of field conformed to PTV, excluding the OARs as much as possible [38].

To optimize the treatment plan, the comparison between rival treatment plans may be performed with the examination of the isodose (2D) and volumetric dose distribution (3D). It should be possible to display axial, sagittal and coronal views in accordance with the physician's prescription. The study and comparison between PTV and OAR DVHs are essential. The procedure with regard to the selection of the treatment plan should be in accordance with dose homogeneity to the PTV, according to ICRU 50 and 62 reports, and with DVHs for OARs. In particular, dose–volume constraints for OARs must be defined, and standard procedures must be followed when the above mentioned constraints cannot be respected. Furthermore, it is necessary to define rules for the written documentation to be attached to the case history, DVH included. Also procedures for the shaping of photon fields, in relation to the system employed, must be standardized. If there is a MLC system, the procedures for data filling must guarantee that the patient's data and the treatment plan belong without doubt to that particular patient [39].

Possible clinical disadvantages of 3D-CRT

Possible clinical disadvantages related to the use of 3DCRT could be due to (i) the increase in the number of marginal relapses; (ii) the increase in the relative volume of the organ exposed to low doses and the possible increase of integral dose. In order to reduce the number of marginal relapses due to the shrinkage of the margins between GTV-CTV-PTV, 3DCRT should be delivered only if [40]:

the microscopic extension of the disease around the GTV is reasonably assessed (good knowledge of the natural history of the tumor to be treated);

the set-up accuracy and, possibly, organ motion effects can be verified with documented evidence;

the imaging is sufficiently suitable for an accurate definition of GTV/CTV.

Further clinical criteria influencing indication for 3D-CRT in clinical practice

All radiotherapy Centers treat a variable number of patients with palliative or symptomatic intent. For those patients, the goal of the treatment is the prompt and effective relief of cancer symptoms. This can be achieved with a less complex treatment delivery technique instead of a more complex one that would delay both the treatment and the benefit expected. Considering non-urgent palliative care programs, it is possible to define a subgroup of patients with intermediate prognosis that could benefit from a more accurate dose distribution or a higher dose delivery with an expected lower toxicity. An example is a metastatic cancer patient with chronic disease, chemo-hormone sensitive tumors with lesions close to OARs (e.g.: spine and marrow, or lymphnodes and bowel). In conclusion, in symptomatic patients, 3D-CRT is non-recommendable, though there is a sub-group of them that could take advantage of this technique [41].

3D-CRT and IMRT in Glioblastoma Treatment

Analysis by Lorentini et al. on 17 GBM patients treated with both 3D-CRT and IMRT showed that IMRT led to better tumor coverage with almost similar dosage to OARs and a significantly low healthy brain irradiation. In this study, patients were subdivided based on whether there was any overlap between PTV and dose-limiting normal tissues. It was seen that there was no statistically significant difference in the doses received by PTV, brainstem or optic apparatus when there was no overlap between two volumes and 3D-CRT in such patients was equally well planned as IMRT. However, differences were noticed between the two plans in case of overlapping volumes where IMRT resulted in significantly low doses to the brainstem and ipsilateral optic apparatus [42].

In a retrospective study by Thibouw et al., 220 patients with GBM treated with 3D-CRT and IMRT. Dosimetric and clinical parameters with survival data were compared between the two. They concluded better dose conformity in those treated by IMRT, although Dmax of the brainstem, optic apparatus and cochlea were higher. The CI in those treated by IMRT in Thibouw et al. was 1.25, which was comparable to our patients treated by 3D-CRT, having a CI of 1.1. In the toxicity analysis, grade 1 and 2 toxicities were significantly higher in the 3D-CRT arm, grade 3 or higher toxicities were more in IMRT, but the frequency was very low and hence not considered significant [43].

However, the CI value is the same as that achieved by IMRT in the analysis by Ibis et al. They concluded lower midline OAR dosage with IMRT and volumetric-modulated arc therapy (VMAT) compared with 3D-CRT. The CI was 2.3 for 3D-CRT, 1.1 for IMRT and 1 for VMAT, which was also achieved in our study by 3D-CRT plans [44].

A study by Wagner et al. has summarized the optimal use of VMAT, IMRT and 3D-CRT with respect to the tumor location. If the PTV is not close to the OARs, then 3D-CRT gives adequate target dose distribution. If PTV and OARs are close, then using IMRT or RapidArc™ (Varian Medical Systems) was advised to attain better homogeneity. Between IMRT and RapidArc, RapidArc had a very short treatment time but resulted in higher low-dose areas. 3D-CRT was also recommended for the younger population due to significantly decreased low-dose volumes [45].

Another study was done retrospectively by Huilgol et al. on 46 patients treated with 60 Gy of 3D-CRT and IMRT showed no difference in overall survival ($p = 0.66$). Thus, treating with intensity-modulated therapies have failed to show any significant improvement in either local control or overall and progression-free survival. Thus, the radiobiological effect is similar to both 3D-CRT and IMRT [46].

Several studies have reported that IMRT including VMAT can achieve high conformity for the target while reducing the dose to organs at risk (OARs), compared with 3DCRT. Sakanaka et al. reported that VMAT could reduce the number of monitor units, while maintaining target coverage comparable with that of IMRT. However, it is difficult to use VMAT for all HGG patients, because it requires a longer preparation time and more human resources compared with 3DCRT [47].

[48] applied 59.4 Gy for GTV plus a margin of 2.5 cm in five patients with GBM in both 3D-CRT and IMRT plans, and 70 Gy for GTV in IMRT with a simultaneous boost in IMRT. They showed that IMRT better preserved normal brain and other critical structures, and that it could be applied simultaneous boost for GTV. [49] compared 3D-CRT and integrated-boost IMRT by using preoperative and postoperative MRI and including perifocal edema around the tumor. The total dose was prescribed for 72 Gy and 60 Gy for PTV1 and PTV2, using daily fractions of 2.4 and 2 Gy. They achieved more homogeneity and conformity with integrated-boost IMRT.

Another similar study was published by Zach et al. [50] They constructed four different treatment plans, including 3DCRT, sequential boost IMRT, integrated-boost IMRT, and tomotherapy, by using two-phase dose definition for 20 high-grade glioma patients. Peritumoral edema was included when defining the treatment volume. At the end of the study, optic chiasm, and ipsilateral glob mean doses were the highest in the 3D-CRT plan, whereas the lowest in integrated-boost IMRT. Contralateral glob mean dose was the highest in tomotherapy plan. The mean of the integral dose to the brain was least with the integrated-boost plan and was lower with IMRT than in 3D-CRT. The researchers reported that the single treatment planning method was not superior to the others. In the present study, the best B-PTV mean dose was achieved with the IMRT plan.

[51] compared IM proton therapy (PRT), VMAT, and 3D-CRT treatment plans in 12 patients with high-grade glial tumors. They used a volume definition containing tumor cavity and edema in postoperative MRI. Compared with 3D-CRT and VMAT, PRT showed a statistically significant dose reduction in whole-brain mean dose, brainstem, pituitary gland, contralateral hippocampus, and contralateral subventricular zone.

[52] performed treatment plan assessment, progression-free survival, and overall survival analysis in patients with high-grade 341 gliomas treated with 3D-CRT and VMAT. They created CTV by

adding an isotropic 10-mm margin to GTV on preoperative contrast-enhanced T1-weighted MRI, the resection cavity on postoperative MRI, and the presence of abnormality FLAIR area, and if present, the residual tumor. They defined PTV by expanding CTV isotropic by 3 mm. They reported that VMAT is superior to 3DCRT in dosimetric and clinical results.

In the first of three studies comparing VMAT and IMRT, [53] evaluated these two planning methods dosimetrically in 10 patients with frontal and temporal high-grade glioma. They defined GTV as contrast-enhancing tumor volume on T1-weighted MRI scans. GTV was expanded by 2 cm; hence, CTV was formed after incorporating postoperative tumor area and T2-weighted MRI (three-dimensionally). CTV was expanded by 0.5 cm to create PTV. They used single-phase plan with 60 Gy in 30 fractions. As a result of the study, PTV coverage, homogeneity, and conformity were found to be similar/equal. They reported a statistically significant decrease in VMAT maximum and mean retinal, intraocular lens, and contralateral optic nerve doses.

No Conflict of interest.

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