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THE POTENTIAL OF 4Π RADIOTHERAPY: A NEW ERA FOR IMPROVING OUTCOMES IN CHALLENGING PAEDIATRIC CASES? A COMPARATIVE DOSIMETRIC ANALYSIS

Presentata da: Costanza Maria Donati

Coordinatore Dottorato

Manuela Ferracin

Supervisore

Alessio Giuseppe Morganti

Co-supervisore

Riccardo Masetti

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1. Introduction

1.1 Clinical Context of Pediatric Radiotherapy

1.2 Conventional Radiotherapy Techniques (VMAT, IMRT)

1.3 Objectives of the Thesis

1.4 Introduction to 4π Technique: Principles and Potential (review)

2. Fundamentals of Pediatric Radiotherapy

2.1 Biological and Clinical Characteristics of Pediatric Tumors

2.2 Therapeutic Challenges: Toxicity, Developmental Considerations, and Risk of Secondary Neoplasms

2.3 Dosimetric Considerations in Pediatric Patients

3. Advanced Techniques in Cranial Radiotherapy

3.1 Intracranial Stereotactic Radiotherapy (SRS)

3.2 CyberKnife (CK): Precision and Limitations in Pediatric Applications

3.3 Comparative Analysis of Techniques: CK, SRS, VMAT, IMRT, and 4π

4. Materials and Methods

4.1 Patient Selection and Clinical Characteristics

4.2 Treatment Planning Using the 4π Technique

4.3 Dosimetric Parameters Evaluated

4.4 Comparative Methodology with VMAT/IMRT Plans

5. Results

5.1 Dose Reduction to Organs at Risk (OARs)

5.2 Homogeneity and Conformity of the Planning Target Volume (PTV)

5.3 Integral Dose Analysis and Clinical Implications

6. Discussion

6.1 Interpretation of Dosimetric Findings

6.2 Clinical Implications for Pediatric Radiotherapy

6.3 Comparison with Literature on CK and SRS

6.4 Study Limitations and Future Perspective

7. Conclusions

7.1 Summary of the Advantages of the 4π Technique

7.2 Recommendations for Future Clinical Studies

7.3 Ethical and Multidisciplinary Considerations

1. Introduction

1.1 Clinical context of paediatric radiotherapy

1.2 Conventional radiotherapy techniques (VMAT and IMRT)

1.3 Objectives of the thesis

1.4 Introduction to the 4π technique: Principles and Potential'

1. Introduction

1.1 Clinical context of paediatric radiotherapy

Radiotherapy remains a cornerstone of the multidisciplinary management of paediatric central nervous system (CNS) malignancies.[1] Despite its proven efficacy in achieving local tumour control, the application of cranial irradiation in children is contraine by the heightened sensitivity of developing tissues and the long-term risk of radiation-induced toxicities. [2] These include neurocognitive deficits, endocrine dysfunction, radionecrosis, and secondary malignancies. The latter are of particular concern given the extended life expectancy of paediatric patients.

1.2 Conventional radiotherapy techniques (VMAT and IMRT)

Compared to earlier techniques, conventional radiotherapy modalities such as intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) significantly improve dose conformality and organ-at-risk (OAR) sparing. However, their coplanar beam arrangements restrict the extent to which dose distributions can be optimised, particularly in anatomically complex or proximity-critical tumour sites. This limitation is particularly pronounced in paediatric neuro-oncology, where minimising collateral damage is of the highest importance.

The 4π radiotherapy technique builds upon the principles of non-coplanar radiation, expanding the potential beam arrangement to a theoretical 4π steradian solid angle. Advanced optimization algorithms such as beam orientation optimization (BOO) and fluence map optimization (FMO) are used to determine collision-free, high-impact beam orientations. Unlike classical non-coplanar techniques, which typically utilise manually selected beams or a small subset of possible orientations, 4π planning explores a vastly larger parameter space. This enables sharper dose gradients around the tumour and improved sparing of OARs, potentially achieving a level of precision that surpasses that of traditional VMAT and IMRT.

The advent of 4π radiotherapy introduces a novel paradigm in treatment planning by leveraging non-coplanar beam trajectories to enhance dose sculpting capabilities. By increasing the freedom of angular beam delivery, 4π techniques can achieve superior conformity indices and reduce the integral dose to healthy tissues. Preliminary dosimetric studies suggest that 4π planning could substantially improve OAR sparing without compromising target coverage, potentially mitigating long-term sequelae in paediatric patients.

1.3 Objectives of the thesis

This thesis presents a comparative dosimetric analysis of 4π radiotherapy versus conventional VMAT/IMRT plans in a cohort of paediatric patients who have previously been treated for intracranial

malignancies. The study aims to quantify differences in the mean dose to critical OARs, evaluate integral dose metrics, and assess the feasibility of delivering 4π plans within clinical constraints. Through this investigation, we will seek to determine whether 4π radiotherapy is a viable and advantageous strategy for improving therapeutic ratios in challenging paediatric cases.

Despite its dosimetric promise, 4π radiotherapy has yet to be widely adopted in clinical practice or comprehensively validated through clinical trials. Criticisms of its feasibility, including concerns about the practicality of achieving true 4π geometry with current linear accelerator designs and the potential for increased integral dose, highlight areas of ongoing debate.

1.4 Introduction to the 4π technique: Principles and Potential'

The project of the thesis started with a narrative review that was conducted in accordance with the SANRA (Scale for the Assessment of Narrative Review Articles) guidelines [6]. This review aimed to evaluate the current body of evidence on 4π radiotherapy, particularly its dosimetric advantages and clinical outcomes. [7]

Synthesis of the review:

This review highlights the substantial potential of 4π radiotherapy as an innovative precision radiation therapy approach. By leveraging non-coplanar beam arrangements, 4π radiotherapy achieves enhanced tumour targeting [8], superior dose conformity [9], and improved sparing of OARs [8–10, 13–15, 17, 24]. These benefits were consistently observed across various cancer types, including glioblastoma multiforme (GBM), head and neck cancers, prostate cancer, and paediatric cases, where long-term side effects are a significant concern. Furthermore, automated planning approaches optimise treatment delivery and address the complexity of beam arrangements [25].

Despite these advancements, the clinical translation of 4π radiotherapy remains limited. Of the included studies, only one prospective clinical trial has demonstrated the feasibility and safety of using 4π radiotherapy to treat patients with recurrent high-grade glioma, with results showing reduced brainstem dose, high patient comfort, and manageable delivery times [18]. However, the small scale of the trial underscores the need for broader validation across diverse patient populations and cancer types.

Furthermore, the feasibility of achieving true 4π geometry has been called into question. Sarkar et al. argued that the physical and geometric constraints of current linear accelerator designs significantly limit the achievable solid angle, particularly for anatomical sites such as the thorax and abdomen [21]. While this critique does not diminish the demonstrated dosimetric advantages, it emphasises the practical challenges of implementing the technique as initially envisaged.

Overall, although the existing evidence demonstrates the dosimetric benefits of 4π radiotherapy, its clinical validation is limited. The findings of Yu et al. provide a valuable starting point, but further prospective trials are needed to evaluate their real-world efficacy and safety. Concurrently, addressing the technical constraints identified by Sarkar et al. will be essential for advancing the technology and broadening its clinical application.

IMRT 4π involves optimising fixed beam angles and intensity modulation to achieve greater precision when treating smaller or irregularly shaped targets [8–16, 20–22, 25], whereas multi-isocentric 4π VMAT uses multiple isocentres and dynamic arc therapy to treat complex or large tumours [17–19, 23, 24, 25]. Both IMRT 4π and multi-isocentric 4π VMAT radiotherapy utilise the full 4π steradian geometry to deliver highly conformal radiation doses, with the aim of maximising tumour coverage while sparing healthy tissues.

Comparison with Other Techniques

Compared to well-established methods such as VMAT and IMRT, 4π radiotherapy offers several significant dosimetric advantages. These include reduced dose spillage [9, 13, 14], sharper dose gradients and OAR sparing [8–10, 12, 14, 15, 17–20, 24, 25]. Although VMAT and IMRT use non-coplanar beams in certain cases, the range of angles they can use is more limited than the comprehensive optimisation possible with 4π. This expanded angular flexibility enables dose escalation in challenging tumours, such as glioblastoma multiforme (GBM) [10] and recurrent head-and-neck cancers [13], without proportional increases in toxicity.

Nevertheless, 4π also introduces challenges. Increased integral dose raises concerns about secondary malignancies, particularly in patients with a long survival time [11]. Indeed, Nguyen et al. compared non-coplanar (4π) beam arrangements with coplanar and VMAT plans, demonstrating that 4π radiotherapy reduces the integral dose in superficial and moderate-depth tumours while sparing OARs. However, it may increase low-dose exposure to normal tissues and the total volumes receiving absorbed doses greater than 2 Gy (e.g., V2Gy), raising concerns about secondary malignancies in long-term survivors. The integral dose may be higher for deep-seated tumours due to the additional beam paths required. While the findings highlight the potential of 4π to improve intermediate and superficial dose reduction, they also emphasise the importance of carefully evaluating long-term risks, particularly in younger or long-surviving patients.

Considerations for paediatric patients

Paediatric patients are a unique and particularly vulnerable group in radiotherapy, where striking the right balance between effectively controlling tumours and minimising long-term risks is critical. Non-coplanar techniques such as 4π radiotherapy show promise in this context, particularly for treating superficial tumours. By utilising optimised non-coplanar beam arrangements, 4π radiotherapy reduces the integral dose to deeper tissues as fewer beam paths intersect normal structures. This is particularly advantageous for children, for whom sparing critical organs and healthy tissues is essential in order to minimise late toxicities. Additionally, 4π radiotherapy offers improved dose conformity and the potential for dose escalation, enabling higher tumour doses to be delivered safely in cases where aggressive control is required.

However, the technique is not without challenges. While 4π reduces the integral dose to deeper tissues, it can increase low-dose exposure to larger volumes of normal tissue due to the wide array of beam angles utilised. This 'low-dose bath' raises concerns about secondary malignancies, which are particularly relevant in paediatric patients given their longer life expectancy and higher sensitivity to radiation-induced late effects. Furthermore, the technical complexity of 4π radiotherapy, such as the need for precise immobilisation and real-time monitoring, can pose difficulties in paediatric patients, necessitating additional preparation and potentially prolonging treatment times.

Taking these considerations into account, 4π radiotherapy should be carefully adapted for paediatric cases. It is particularly well-suited to children with superficial tumours, as its ability to minimise the dose to deeper tissues can be maximised in these cases. Advanced planning algorithms and dose optimisation tools should be used to limit low-dose spread while maintaining high conformality. Additionally, robust immobilisation and verification protocols are essential for precise delivery and to avoid errors inherent in the complexity of non-coplanar plans.

In summary, further research and modelling of secondary tumour risks are necessary to fully understand and mitigate these challenges, ensuring the safe and effective use of 4π radiotherapy in paediatric patients.

Table 1: Summary of characteristics and results of the studies included in the analysis

Authors, year	Aims	Key methods	Results	Conclusion
Dong, 2013 [8]	Assess improvements in lung SBRT with 4π	12 patients, comparison with IMRT & VMAT	Improved tumor coverage (+12%), reduced max doses to critical organs (up to 72%), and lower R50.	4π improved tumor targeting and critical organ sparing.
Dong, 2013 [9]	Evaluate liver SBRT with 4π	10 patients, comparison with VMAT	Reduced mean liver dose (-31%) and doses to kidneys, stomach, and spinal cord (-50% to -70%).	4π enhanced dose gradient and OAR sparing for liver SBRT.
Nguyen, 2014 [10]	Explore dose escalation for GBM	11 patients, comparison with clinical plans	Dose gradients improved (>20% R50 reduction), significant reductions in max/mean OAR doses.	4π enabled safe dose escalation with better dose conformity.
Nguyen, 2014 [11]	Impact of 4π on lung/liver SBRT	22 patients, non-coplanar vs. coplanar	Reduced integral dose for smaller tumors; higher low-dose exposure to normal tissue.	Highlights benefits but notes caution for low-dose exposure.
Dong, 2014 [12]	Feasibility of prostate cancer	12 patients, VMAT vs. 4π	Reduced rectal/bladder doses (-11% to -50%), lower mean body dose.	4π achieved superior dosimetry for prostate cancer.
Rwigema, 2015 [13]	Apply 4π to head-and-neck SBRT	27 tumors, dose-escalation study	Reduced OAR doses (10%-89%), dose escalation feasible (+10-20 Gy) with improved tumor control.	4π allowed dose escalation while sparing critical structures.
Woods, 2016 [14]	Quantify liver SBRT benefits	20 patients, 4π vs. coplanar/non-coplanar	Reduced liver volume exposed to >15 Gy, better normal tissue complication profile.	4π provided safer dose escalation for liver SBRT.
Tran, 2017 [15]	Compare IMPT, 4π, and VMAT for prostate	10 patients, multi-modality comparison	IMPT better homogeneity; 4π superior in rectum/bladder sparing vs. VMAT.	4π excelled in OAR sparing for prostate cases.
Chen, 2017 [16]	Pediatric rhabdomyosarcoma case	1 case, IMPT vs. VMAT & 4π	IMPT superior in sparing optic structures, all plans conformal.	IMPT is better for optic sparing; 4π achieved acceptable results.
Subramanian, 2017 [17]	Complex head-and-neck targets	25 patients, VMAT vs. 4π VMAT	Reduced doses to parotids, brainstem, and pharyngeal muscles with 4π VMAT.	4π VMAT provided consistent dosimetric improvements.
Yu, 2018 [18]	Assess the feasibility of glioma	11 patients, recurrent glioma cases	Reduced brainstem dose (-2.92 Gy), enhanced dosimetry, good patient comfort (8.6/10).	Feasible and effective for glioma with safe dose delivery.
Woods, 2018 [19]	Hearing preservation in acoustic neuroma	30 patients, comparison with IMRT/SRS/SRT	Reduced cochlear and brainstem doses (15%-32%), improved long-term hearing preservation.	4π improved hearing outcomes compared to conventional methods.
Lyu, 2018 [20]	Efficiency of 4π VMAT	9 patients, 4π vs. 2π VMAT	Reduced OAR mean/max doses (-9.63%/-3.08%), lower R50 (-23%).	4π VMAT improved dosimetry and efficiency.
Sarkar, 2019 [21]	Assess the feasibility of 4π geometry with current machines	Theoretical surface integral-based analysis	The maximum achievable solid angle is significantly less than 4π with current linear accelerator designs.	Current cantilever designs cannot achieve true 4π geometry.
Landers, 2019 [22]	Automated 4π planning	40 patients (lung & head-and-neck)	Improved plan quality with knowledge-based methods (PQM +2.6%).	Automation enhanced 4π consistency and quality.
MacDonald, 2020 [23]	Optimization of beam angles	8 cranial cases, comparison with VMAT	Reduced brainstem max dose (-2.63 Gy), improved metrics with optimized couch/collimator angles.	Optimized beam arrangements enhanced clinical metrics.
Reis, 2021 [24]	SBRT for ventricular tachycardia	15 patients, dose sparing in cardiac OARs	Mean dose reductions: esophagus (-19%), spinal cord (-33%), liver (-59%), lungs (-19%).	4π significantly reduced doses to critical cardiac structures.
Rossi, 2021 [25]	Autoplanning for lymphoma	25 patients, coplanar vs. non-coplanar	Non-coplanar plans reduced heart Dmean and lung high doses.	Non-coplanar planning favored critical structure protection.

Legend: 4π: Advanced non-coplanar radiotherapy technique; 2π: Coplanar volumetric modulated arc therapy; BAO: Beam Angle Optimization; CBA: Coplanar Beam Arrangement; CI: Conformity Index; Dmean: Mean Dose; D2%: Dose to 2% of the volume; GBM: Glioblastoma; Gy: Gray; IMPT: Intensity-Modulated Proton Therapy; IMRT: Intensity-Modulated Radiation Therapy; NCBA: Non-Coplanar Beam Arrangement; NTCP: Normal Tissue Complication Probability; OARs: Organs at Risk; PQM: Plan Quality Metric; PTV: Planning Target Volume; R50: 50% Dose Spillage Metric; SBRT: Stereotactic Body Radiation Therapy; SRS: Stereotactic Radiosurgery; SRT: Stereotactic Radiation Therapy; TCP: Tumor Control Probability; VMAT: Volumetric Modulated Arc Therapy

Table 2: Detailed characteristics and results of the analyzed studies

Authors, Year [Ref]	Aims	Methods	Results	Conclusion
Dong, 2013 [8]	Assess dosimetric improvements in SBRT for larger/central lung tumors using 4π planning	12 patients with centrally located/larger lung tumors. Compared IMRT, VMAT, and 4π plans. 50 Gy dose with a dose escalation study	4π plans: - Reduced max doses to heart (32%), esophagus (72%), trachea (37%), bronchus (44%), and spinal cord (53%) ($P \leq 0.001$). - R50 reduced by >50%. - Lung V20, V10, V5 reduced by 64%, 53%, 32% ($P \leq 0.001$). - PTV doses increased by 12% ($P = 0.002$).	4π plans significantly improved tumor coverage and critical organ sparing compared to VMAT and IMRT.
Dong, 2013 [9]	Improve liver SBRT using 4π planning	10 liver SBRT cases, previously treated with 50-60 Gy in 5 fractions using VMAT	4π vs VMAT: - Reduced 50% dose spillage by 22%, integral dose by 19%. - Mean liver dose reduced by 31%. - Left kidney (-70%), right kidney (-51%), stomach (-67%), spinal cord (-64%) doses reduced ($P < 0.05$).	The 4π technique significantly improved dose gradient and organ sparing compared to VMAT.
Nguyen, 2014 [10]	Feasibility of dose escalation for GBM while maintaining normal tissue tolerance using 4π	11 GBM patients, previously treated with VMAT at 59.4-60 Gy	4π vs clinical plans: - Dose gradients improved (>20% R50 reduction). - Max/mean doses significantly reduced ($P < 0.05$) by 47.01-98.82% (max) and 51.87-99.47% (mean). - No significant change in non-brain OAR doses.	4π substantially increased dose gradients outside the PTV while sparing critical organs.
Nguyen, 2014 [11]	Investigate the impact of 4π radiotherapy on lung/liver SBRT	22 SBRT patients (lung/liver)	- Non-coplanar beams reduced integral doses for tumors <10 cm. - Increased V2 for non-coplanar plans.	Larger normal tissue exposure to low doses with non-coplanar beams needs careful risk/benefit evaluation.
Dong, 2014 [12]	Assess the feasibility of 4π therapy for prostate cancer on a C-arm linac	12 low-risk prostate cancer patients treated with VMAT (40 Gy in 5 fractions)	4π vs VMAT: - Reduced rectum doses (V50%, V80%, V90%, D1cc) by 50%, 28%, 19%, and 11% ($P < 0.005$). - Reduced mean body dose (from 2.07 Gy to 1.75 Gy, $P = 0.0001$). - Slight bladder dose reduction.	4π therapy provided superior prostate treatment plan quality compared to VMAT.
Rwigema, 2015 [13]	Explore 4π for recurrent/metastatic head-and-neck cancer SBRT	27 patients with 29 tumors (median dose 44 Gy in 5 fractions)	- OAR doses reduced by 22%-89% (mean), 10%-86% (max). - 50% dose spillage reduced by 33%. - PTV dose escalation (+10 Gy, +20 Gy) achievable without increasing OAR doses. - Predicted TCP increased to 85.5%-91.4% (10-20 Gy escalation). - Grade 3 late toxicity: 7.4%.	4π plans allowed for significant dose escalation while sparing critical organs.
Woods, 2016 [14]	Quantify dosimetric benefits and normal tissue toxicity limits for liver SBRT	20 liver patients treated with 30-60 Gy using coplanar VMAT, replanned with non-coplanar VMAT and 4π	4π vs cVMAT/nVMAT: - Reduced liver volume receiving >15 Gy. - 50% dose spillage reduced by ~23%. - Higher tolerable doses for all NTCP limits ($P < 0.05$).	4π offered superior OAR sparing and allowed clinically relevant dose escalation.
Tran, 2017 [15]	Compare IMPT, 4π, and VMAT for prostate cancer	10 patients (79.2 Gy total dose)	4π vs IMPT: - Lower anterior rectal wall doses. - Lower V40-V80 for rectum. IMPT vs 4π: - Lower bladder/rectum doses but higher femoral head doses. - More homogenous doses in IMPT.	IMPT superior in dose homogeneity, while 4π better at sparing rectum/bladder compared to VMAT.
Chen, 2017 [16]	Case report of IMPT in pediatric rhabdomyosarcoma	1 pediatric case, compared IMPT, VMAT, and 4π	IMPT vs 4π: - Better sparing of retina, lens, lacrimal gland. - Conformal dose coverage for all plans.	IMPT provided better sparing of optic structures, reducing long-term neurocognitive risks.

Subramanian, 2017 [17]	Feasibility of MI4π-VMAT for complex head-and-neck cancer targets	25 HNC patients, replanned with coplanar VMAT and non-coplanar MI4π-VMAT	MI4π-VMAT vs VMAT: - Reduced mean doses to parotids (-3 Gy), larynx (-4 Gy), oral cavity (-5 Gy), and pharyngeal muscles (-4.3 Gy). - Reduced max doses to brainstem (-6.0 Gy), spinal cord (-3.8 Gy), and oral cavity (-2.4 Gy).	MI4π-VMAT achieved reliable dosimetric improvements, sparing key OARs.
Yu, 2018 [18]	Clinical feasibility and dosimetric benefits of 4π radiotherapy	11 recurrent high-grade glioma patients	4π vs VMAT: - Reduced mean/max OAR doses. - Brainstem max dose reduced by 2.92 Gy, enabling safer treatments. - Patient comfort rated 8.6/10.	4π demonstrated feasibility, safety, and patient comfort with superior dosimetry.
Woods, 2018 [19]	Investigate 4π radiation therapy to spare the cochlea and improve hearing preservation in acoustic neuroma treatment	30 patients with acoustic neuroma (SRS, SRT, IMRT plans)	4π vs SRS, SRT, IMRT: - Cochlea mean dose reduced by 32% (SRS), 29% (SRT), and 32% (IMRT). - Brainstem max dose reduced by 1.6 Gy (20%) for SRS, 2.2 Gy (15%) for SRT, and 7.1 Gy (18%) for IMRT. - Lower NTCP for hearing loss at 3 years (30.8% vs 40.8%) and 5 years (43.3% vs 61.7%).	4π significantly reduced OAR doses, improving hearing preservation in acoustic neuroma treatment.
Lyu, 2018 [20]	Achieve dosimetric quality and delivery efficiency with 4πVMAT	9 patients (brain, lung, prostate cancer), compared 4πVMAT vs 2πVMAT	4πVMAT vs 2πVMAT: - Reduced OAR mean/max doses by 9.63% and 3.08% respectively. - R50 reduced by 23%. - Max doses to critical OARs (brainstem, vessels, bronchus) reduced by 64.8%, 41.5%, and 55.5% respectively.	4πVMAT improved dosimetry and delivery efficiency compared to 2πVMAT.
Sarkar, 2019 [21]	Assess the feasibility of 4π geometry with current machines	Theoretical surface integral-based analysis	The maximum achievable solid angle is significantly less than 4π with current linear accelerator designs.	Current cantilever designs cannot achieve true 4π geometry.
Landers, 2019 [22]	Develop automated 4π treatment planning using evolving knowledge-base (EKB)	20 lung and 20 head-and-neck (HN) patients, evaluated for plan quality with a PQM points system	Lung cases: - EKB plans had significantly higher PQM (+2.60%) than manually created 4π. HN cases: - EKB plans comparable to manual 4π, but lower PQM compared to automated plans using a high-quality training set.	EKB allows for improved plan quality through automation in 4π planning.
MacDonald, 2020 [23]	Develop a novel system for patient-specific optimization of couch, collimator, and gantry angles for VMAT	8 cranial targets in test-patient anatomy, compared CODA plans vs standard VMAT	CODA plans vs VMAT: - OAR max dose reduced by 20.6% ($P < 0.01$). - Brainstem max dose decreased by 2.63 Gy ($P = 0.031$).	CODA-based optimization improved multiple clinical metrics compared to standard VMAT.
Reis, 2021 [24]	Investigate the benefits of 4π-optimized trajectories in SBRT for ventricular tachycardia (VT-SBRT)	15 patients (thorax CT), comparison of dose sparing in OARs (25 Gy in a single fraction)	- Max dose reductions: esophagus (18%), spinal cord (26%), trachea (22%). - Mean dose reductions: esophagus (19%), spinal cord (33%), liver (59%), lungs (19%), trachea (43%). - Median dose reductions observed across multiple organs (up to 72%).	4π provided significant reductions in mean and median doses to cardiac structures, without reducing the maximum dose.
Rossi, 2021 [25]	Compare coplanar and non-coplanar beam configurations using autoplanning in lymphoma	25 female patients (mediastinal lymphoma), 24 plans generated (11 coplanar, 11 non-coplanar)	- Non-coplanar plans produced highly conformal plans, reduced high doses to lungs, and decreased heart Dmean. - B-VMAT reduced the low-dose spread to the lungs and left breast.	Non-coplanar configurations were favorable in reducing critical doses for lymphoma patients.

Legend: 4π: Advanced non-coplanar radiotherapy technique; 2π: Coplanar volumetric modulated arc therapy; BAO: Beam Angle Optimization; CBA: Coplanar Beam Arrangement; CI: Conformity Index; Dmean: Mean Dose; D2%: Dose to 2% of the volume; GBM: Glioblastoma; Gy: Gray; IMPT: Intensity-Modulated Proton Therapy; IMRT: Intensity-Modulated Radiation Therapy; NCBA: Non-Coplanar Beam Arrangement; NTCP: Normal Tissue Complication Probability; OARs: Organs at Risk; PQM: Plan Quality Metric; PTV: Planning Target Volume; R50: 50% Dose Spillage Metric; SBRT: Stereotactic Body Radiation Therapy; SRS: Stereotactic Radiosurgery; SRT: Stereotactic Radiation Therapy; TCP: Tumor Control Probability; VMAT: Volumetric Modulated Arc Therap

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2. Fundamentals of Paediatric Radiotherapy

2.1 Biological and clinical characteristics of paediatric tumours

2.2 Therapeutic challenges: Toxicity, developmental considerations, and risk of secondary neoplasms

2.3 Dosimetric considerations in paediatric patients

2. Fundamentals of Paediatric Radiotherapy

2.1 Biological and clinical characteristics of paediatric tumours

Paediatric central nervous system (CNS) tumours are the most common solid malignancies in children and differ markedly from adult brain tumours in terms of histopathology, molecular drivers, and clinical behaviour. Common types include medulloblastoma, ependymoma, high-grade glioma, and atypical teratoid/rhabdoid tumour, each of which is associated with a distinct developmental origin and genetic alteration. Advances in molecular profiling have led to more refined classifications and treatment protocols adapted to risk, improving survival rates for certain subtypes while highlighting the need to mitigate the long-term side effects of therapy [1][2].

As these tumours often arise in anatomically sensitive regions, their management requires careful consideration of neurodevelopmental and endocrine functions. Paediatric tumours typically exhibit higher proliferative indices and radiosensitivity, which can be therapeutically advantageous. However, the immature physiology of children, particularly about brain plasticity, hormonal regulation, and tissue repair, renders them more vulnerable to radiation-induced damage [3].

2.2 Therapeutic challenges: Toxicity, developmental considerations, and risk of secondary neoplasms

Radiotherapy in paediatric oncology poses unique challenges due to the increased vulnerability of developing tissues to ionising radiation. Acute toxicities may include mucositis, alopecia, myelosuppression, and transient neurological symptoms, while late effects may include neurocognitive decline, endocrine dysfunction, sensorineural hearing loss, radionecrosis, and cerebrovascular complications [4]. The risk of secondary malignancies is of particular concern, with latency periods extending beyond two decades and incidence rates that are significantly higher than in adults [5, 6].

The probability of radiation-induced secondary tumours correlates with the total dose, the volume of irradiated tissue, and the patient's age at the time of exposure. Survivors of childhood cancer face a lifelong risk of developing subsequent neoplasms, including second malignant neoplasms (SMNs). This risk varies depending on treatment era, follow-up duration, and study design. The following data summarizes cumulative incidence rates reported in both prospective and retrospective studies.

In a prospective cohort study by Mertens et al. [7], the cumulative incidence of subsequent neoplasms was 18.6% at 20 years of follow-up, decreasing to 3.5% at 30 years. Friedman et al. [8] reported a 30-year cumulative incidence of 20.5% for all subsequent neoplasms and 7.9% for SMNs in a similar prospective analysis.

Retrospective studies provide additional context. Neglia et al. [9] found a 20-year cumulative incidence of SMNs at 3.2%. Meadows et al. [10] reported that, at 30 years, the cumulative incidence of SMNs reached 9.3%, with nonmelanoma skin cancer accounting for 6.9%.

These findings underscore the importance of long-term surveillance and risk-adapted follow-up strategies for childhood cancer survivors. Differences in incidence rates across studies may reflect variations in treatment modalities, diagnostic criteria, and cohort characteristics. Continued research is essential to refine survivorship care and mitigate late effects [7-10]. These risks emphasise the importance of precision in treatment planning and long-term survivorship care.

2.3 Dosimetric considerations in paediatric patients

Dosimetric planning in paediatric radiotherapy must balance optimal tumour coverage with maximum preservation of healthy tissues. Organs at risk (OARs), including the hippocampi, optic nerves, pituitary gland, cochleae, and brainstem, require stringent dose constraints due to their critical roles in development and function. Integral dose, which is defined as the total energy deposited in non-target tissues, is a key metric that is linked to systemic toxicity and secondary cancer risk [11].

Although advanced modalities such as IMRT and VMAT improve dose conformality, their coplanar beam arrangements may limit sparing in complex anatomical scenarios. Emerging techniques such as 4π radiotherapy, which utilise non-coplanar beam trajectories, offer enhanced spatial modulation and reduced integral dose, potentially improving therapeutic ratios in paediatric patients [12]. Even modest dosimetric improvements can yield significant clinical benefits in this vulnerable population, underscoring the importance of ongoing comparative studies and personalised planning strategies.

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3. Advanced Techniques in Cranial Radiotherapy

3.1 Intracranial stereotactic radiotherapy (SRS)

3.2 CyberKnife (CK): Precision and limitations in paediatric applications

3.3 Comparative analysis of techniques: CK, SRS, VMAT, IMRT, and 4π

3. Advanced Techniques in Cranial Radiotherapy

3.1 Intracranial stereotactic radiotherapy (SRS)

Stereotactic radiosurgery (SRS), originally developed with cobalt-60 platforms, has been used since the 1950s to deliver high-dose radiation to intracranial targets with surgical precision and reduced toxicity compared to surgical approaches [1]. Technological advancements over time have enabled both frame-based and frameless mask-guided systems to deliver single or multifraction treatments with submillimetric accuracy.

While most clinical data on SRS originates from adult populations, its application in paediatric neuro-oncology has steadily increased over the past two decades [2]. The appeal of SRS for use in children lies in its ability to limit the size of the radiation field and reduce the dose to the parenchyma of the brain, thereby minimising late toxicities such as neurocognitive impairment [3], neurohormonal dysfunction [4], and secondary malignancies [5]. While the estimated risk of secondary neoplasms post-SRS in adults is low (0.045% over 10 years), paediatric-specific data remain limited and warrant further investigation [6].

Most paediatric SRS treatments have employed single-fraction protocols, although multifraction regimens (three to five fractions) are increasingly being used for larger lesions [7]. A recent meta-analysis by Murphy et al. [8] reviewed 68 studies involving around 400 paediatric patients and confirmed acceptable local control rates for both benign and malignant intracranial tumours. Reported control rates include 60–100% for gliomas, 50–70% for medulloblastomas, and 30–90% for ependymomas [9–12]. These findings support the judicious use of SRS in recurrent or refractory paediatric brain tumours, particularly when conventional radiotherapy has already been exhausted.

3.2 CyberKnife (CK): Precision and limitations in paediatric applications

The CyberKnife (CK) system is a frameless robotic radiosurgery device that delivers high-dose radiation with real-time image guidance and submillimetric precision. Its ability to track tumour motion during treatment makes it particularly suitable for paediatric patients, who may require anaesthesia or have difficulty remaining still. The non-invasive nature of CK and its hypofractionated delivery shortens the overall treatment duration, improving the procedure's feasibility in paediatric settings. Additionally, the absence of rigid frames enhances patient comfort and reduces procedural anxiety.

Despite these advantages, CK has limitations. The system’s high acquisition and maintenance costs restrict its availability, and individual treatment sessions may be prolonged due to complex setup and imaging requirements. CK may also be less effective for large or irregularly shaped tumours, requiring a greater number of beams and increasing low-dose exposure to surrounding tissues [13].

Our narrative review confirms that the evidence supporting CK in paediatric neuro-oncology remains limited [14]. Most of the available data originate from single-case reports or small case series involving head and neck tumours. Only three studies included cohorts of between five and 52 patients, and just one of these studies provided an actuarial analysis. This analysis reported a 92% three-year local control rate despite the use of a margin-free technique. Severe complications were rare, with bone necrosis observed in only one re-irradiated patient [15-27].

A major concern with CK is the 'dose bath' phenomenon, whereby low-dose radiation is distributed across larger volumes of the body due to the system's broad beam penumbra and multiple beam angles. This is particularly problematic in paediatric patients, whose developing tissues are more susceptible to radiation-induced damage. As demonstrated by Paddick et al.[13], cumulative exposure to low doses of radiation may increase the risk of

secondary malignancies over time. The longer life expectancy of paediatric patients further amplifies this risk, as radiation-induced mutations have more time to manifest.

3.3 Comparative analysis of techniques: CK, SRS, VMAT, IMRT, and 4π.

Each radiotherapy modality has distinct advantages and limitations in a paediatric context. Conventional techniques, such as VMAT and IMRT, offer excellent dose conformality and are widely used in paediatric neuro-oncology. However, their coplanar beam arrangements may limit the sparing of critical structures in anatomically complex cases.

SRS and CK provide highly conformal dose distributions and are particularly useful for treating small, well-defined lesions. SRS is supported by extensive adult and emerging paediatric data [7-8], while CK offers additional flexibility in beam delivery and patient positioning. Nevertheless, both techniques carry a risk of low-dose exposure to surrounding tissues, with CK being more susceptible to dose-bath effects due to its delivery geometry [12].

The 4π radiotherapy technique is a novel approach that uses non-coplanar beam trajectories to optimise dose sculpting. By expanding the angular range of beam entry, 4π can achieve superior conformity and reduce the integral dose compared to volumetric-modulated arc therapy (VMAT) and intensity-modulated radiation therapy (IMRT). Preliminary dosimetric analyses suggest that 4π radiotherapy may offer enhanced organ-at-risk sparing and improved homogeneity in the planning target volume (PTV), making it a promising option for complex paediatric cases.

In summary, while CK and SRS offer precision and reduced treatment burden, their use in paediatric patients must be carefully considered in relation to potential long-term risks. The emergence of 4π radiotherapy introduces a compelling alternative that warrants further investigation through comparative clinical trials and long-term outcome studies.

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4. Materials and Methods

4.1 Patient Selection and Clinical Characteristics

4.2 Treatment Planning Using the 4π Technique

4.3 Dosimetric Parameters Evaluated

4.4 Comparative Methodology with VMAT/IMRT Plans

4. Materials and Methods

4.1 Patient Selection and Clinical Characteristics

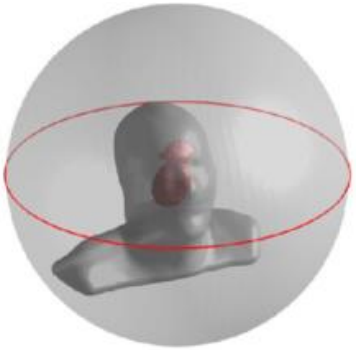
This retrospective dosimetric study included ten pediatric patients previously treated with cranial radiotherapy between 2019 and 2025. The cohort comprised individuals aged between 1 and 17 years, with histologically confirmed diagnoses of ependymoma (n = 4), medulloblastoma (n = 2), high-grade gliomas (n = 2), and atypical teratoid/rhabdoid tumor (n = 2). All patients had undergone initial treatment using either volumetric modulated arc therapy (VMAT) or intensity-modulated radiotherapy (IMRT), with a prescribed total dose of 54 Gy delivered in 30 fractions (1.8 Gy per fraction).

Clinical data, including tumor location, staging, and prior treatment parameters, were extracted from institutional records. Inclusion criteria required the availability of complete imaging datasets and treatment plans suitable for re-planning using the 4π technique. Ethical approval for the retrospective analysis was obtained in accordance with institutional guidelines.

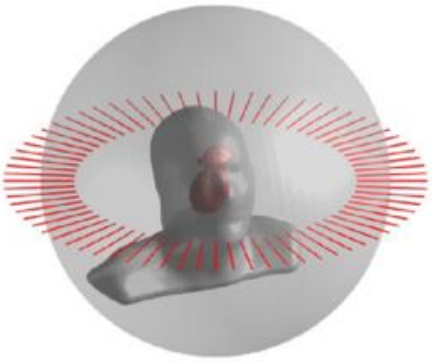
4.2 Treatment Planning Using the 4π Technique

For each patient, a novel treatment plan was generated using the 4π radiotherapy approach. This technique employed five non-coplanar partial arcs strategically selected to optimize dose conformality and minimize exposure to surrounding healthy tissues. Beam angles were chosen to maximize spatial separation between target volumes and organs at risk (OARs), leveraging the expanded angular freedom characteristic of 4π planning.

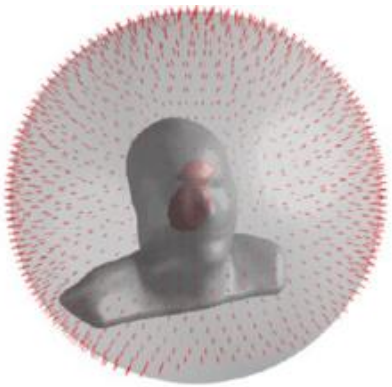
Treatment planning was performed using a clinically validated planning system capable of supporting non-coplanar arc optimization. All plans were normalized to ensure equivalent target coverage compared to the original VMAT/IMRT plans. Dose constraints for critical OARs were applied in accordance with pediatric radiotherapy guidelines, and plan deliverability was verified through standard quality assurance protocols.



co-planar VMAT

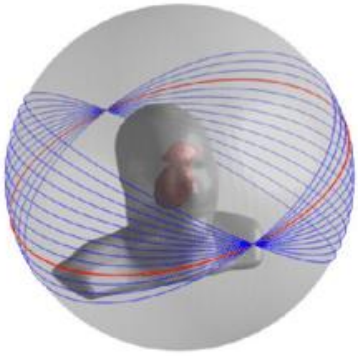


Multiple modulated beams



4π

(separated beams)



4π

(non co-planar VMAT)

The updated treatment protocols were designed in compliance with established paediatric dose constraints for organs at risk, as outlined in contemporary clinical practice guidelines.

Table 1:

	Medulloblastoma HR (quartet) Conventional fractionation	NCCN Paediatric Diffuse High grade gliomas 2025	NCCN Paediatric Medulloblastoma 2025	Ependimoma II
Optic chiasm	Mandatory: V50.4 Gy < 50% D2% < 54 Gy	Dmax< 54Gy	Dmax< 54Gy	Dmax< 54Gy
Optic nerves	V54 Gy < 70%	Dmax< 54Gy	Dmax< 54Gy	
Brainstem	D2% < 45 Gy	Dmax<52.4 Gy	Mean dose < 54 Gy	V59.4Gy< 66G%
Hypothalamus	ALARA	Mean dose < 25 Gy	Mean dose < 25 Gy	
Pituitary	ALARA	Mean dose < 25 Gy	Mean dose < 25 Gy	
Cochlea		D50%< 35 Gy; D50% <20Gy preferred - single cochlea	Mean dose < 30 Gy	Mean dose < 30 Gy

4.3 Dosimetric Parameters Evaluated

Based on the review we conducted on the 4π technique, we identified the parameters commonly analysed in studies involving paediatric patients and patients with cerebral targets. Our analysis began by focusing on the following metrics: Average Maximum Dose to Organs at Risk (OAR), and Average Mean Dose to OAR and, R50 reduction (Table 2).

Table 2:

Authors, Year [Ref]	**Aims**	**Methods**	**Results**	**Conclusion**
Nguyen, 2014 [1]	Feasibility of dose escalation for GBM while maintaining normal tissue tolerance using 4π	11 GBM patients, previously treated with VMAT at 59.4-60 Gy	4π vs clinical plans: - Dose gradients improved (>20% R50 reduction). - Max/mean doses significantly reduced (P < 0.05) by 47.01-98.82% (max) and 51.87-99.47% (mean). - No significant change in non-brain OAR doses.	4π substantially increased dose gradients outside the PTV while sparing critical organs.
Chen, 2017 [2]	Case report of IMPT in pediatric rhabdomyosarcoma	1 pediatric case, compared IMPT, VMAT, and 4π	IMPT vs 4π: - Better sparing of retina, lens, lacrimal gland. - Conformal dose coverage for all plans.	IMPT provided better sparing of optic structures, reducing long-term neurocognitive risks.
Yu, 2018 [3]	Clinical feasibility and dosimetric benefits of 4π radiotherapy	11 recurrent high-grade glioma patients	4π vs VMAT: - Reduced mean/max OAR doses. - Brainstem max dose reduced by 2.92 Gy, enabling safer treatments. - Patient comfort rated 8.6/10.	4π demonstrated feasibility, safety, and patient comfort with superior dosimetry.
Lyu, 2018 [4]	Achieve dosimetric quality and delivery efficiency with 4πVMAT	9 patients (brain, lung, prostate cancer), compared 4πVMAT vs 2πVMAT	4πVMAT vs 2πVMAT: - Reduced OAR mean/max doses by 9.63% and 3.08% respectively. - R50 reduced by 23%. - Max doses to critical OARs (brainstem, vessels, bronchus) reduced by 64.8%, 41.5%, and 55.5% respectively.	4πVMAT improved dosimetry and delivery efficiency compared to 2πVMAT.
MacDonald, 2020 [5]	Develop a novel system for patient-specific optimization of couch, collimator, and gantry angles for VMAT	8 cranial targets in test-patient anatomy, compared CODA plans vs standard VMAT	CODA plans vs VMAT: - OAR max dose reduced by 20.6% (P < 0.01). - Brainstem max dose decreased by 2.63 Gy (P = 0.031).	CODA-based optimization improved multiple clinical metrics compared to standard VMAT.

For organs at risk, the following structures were analysed:

- Optic nerves
- Optic chiasm
- Pituitary gland
- Hypothalamus
- Cochleae
- Brainstem

For the planning target volume (PTV), parameters assessed included:

- Mean dose (D_mean)
- Maximum dose (D_max)
- Homogeneity index (HI)
- Conformity index (CI)

Key metrics included mean dose, maximum dose, and volume receiving ≥20 Gy (V20). Additionally, the integral dose—defined as the total energy deposited in non-target tissues—was calculated for each plan to assess systemic exposure and potential long-term toxicity.

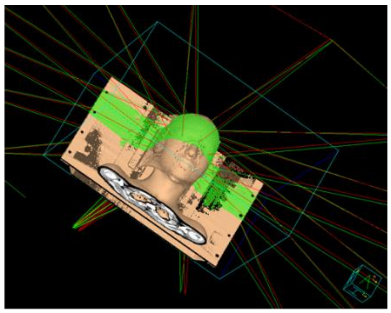
4.4 Comparative Methodology with VMAT/IMRT Plans

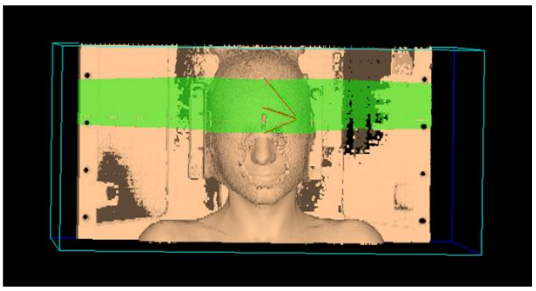
Each 4π plan was directly compared to the patient's original VMAT or IMRT plan using a standardized scorecard approach. Comparative analysis included:

- Percentage reduction in mean dose to OARs
- Improvement in PTV homogeneity and conformity
- Changes in integral dose

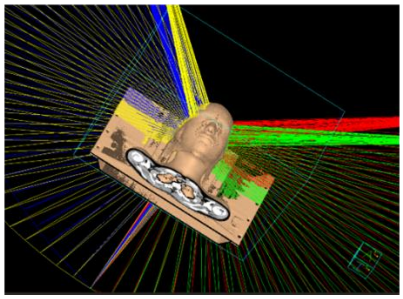
Statistical analysis was performed to quantify dosimetric differences between techniques. Descriptive statistics were used to summarize findings across the cohort, and paired comparisons were conducted to evaluate the significance of observed improvements. All plans were reviewed by a multidisciplinary team, including radiation oncologists and medical physicists, to ensure clinical relevance and feasibility.

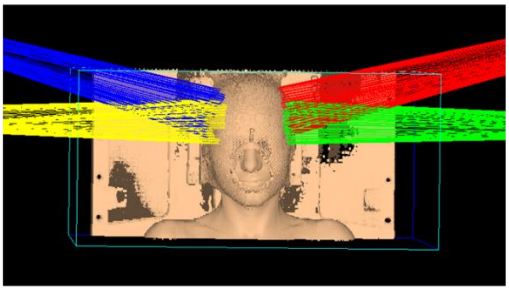
co-planar VMAT





4π
(non co-planar VMAT)





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5. Results

5.1 Dose Reduction to Organs at Risk (OARs)

5.2 Homogeneity and Conformity of the Planning Target Volume (PTV)

5.3 Integral Dose Analysis and Clinical Implications

5. Results

The analysis focuses on key metrics including homogeneity index (HI), conformity index (CI), mean dose reduction to organs at risk (OARs), and integral dose. All statistical comparisons were performed using paired analyses, and p-values were reported to assess significance.

5.1 Dose Reduction to Organs at Risk (OARs)

Quantitative comparisons were performed for average mean and maximum doses to critical OARs, including the optic nerves, optic chiasm, cochleae, hypothalamus, pituitary gland, and brainstem. The analysis revealed consistent dose reductions across multiple structures in the 4π plans.

- ✓ Dosimetric Comparison of Optic Nerve Exposure

  Left Optic Nerve (OpticNerveL)

- The maximum dose delivered to the left optic nerve was significantly lower in the 4π plan (4.895 Gy) compared to the VMAT plan (9.125 Gy), with a p-value of 0.0147. This statistically significant reduction suggests that the 4π technique may offer superior protection against radiation-induced optic neuropathy by minimizing high-dose exposure to this critical structure.
- The mean dose to the left optic nerve was also reduced in the 4π plan (3.275 Gy) relative to the VMAT plan (6.475 Gy). Although the observed p-value of 0.0603 does not meet conventional thresholds for statistical significance, the trend indicates a potential dosimetric advantage.

  Right Optic Nerve (OpticNerveR)

- The 4π technique yielded a mean dose of 4.175 Gy to the right optic nerve, compared to 7.2525 Gy in the VMAT plan. The difference was statistically significant ($p = 0.0367$), underscoring the efficacy of the 4π approach in reducing radiation exposure to organs at risk (OARs) and reinforcing its potential for enhanced neuro-ocular sparing.

- ✓ Dosimetric Comparison of Cochleae
  Although the data is not statistically significant, it can be seen that, in particular in the left cochlea, there is greater preservation with non-coplanar beam geometry.

The pituitary gland and brainstem, using the 4πtechnique, are kept within paediatric dosage limits. Furthermore, although the data is not statistically significant, the average dose to the pituitary gland is significantly lower in the non-coplanar plan.

The 4π technique demonstrated superior sparing of critical structures, which may translate into reduced risk of neuroendocrine and sensory complications.

Figure 1:

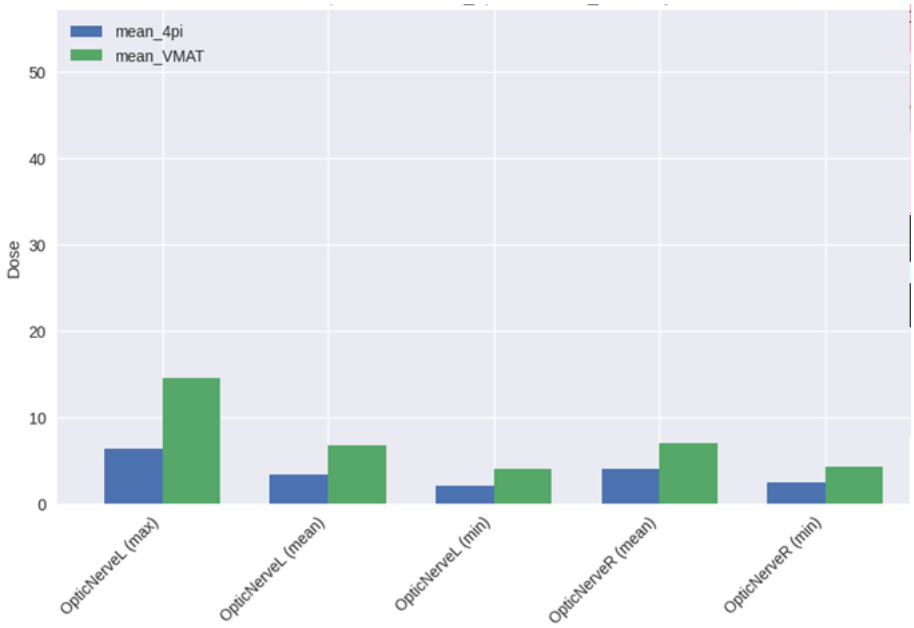
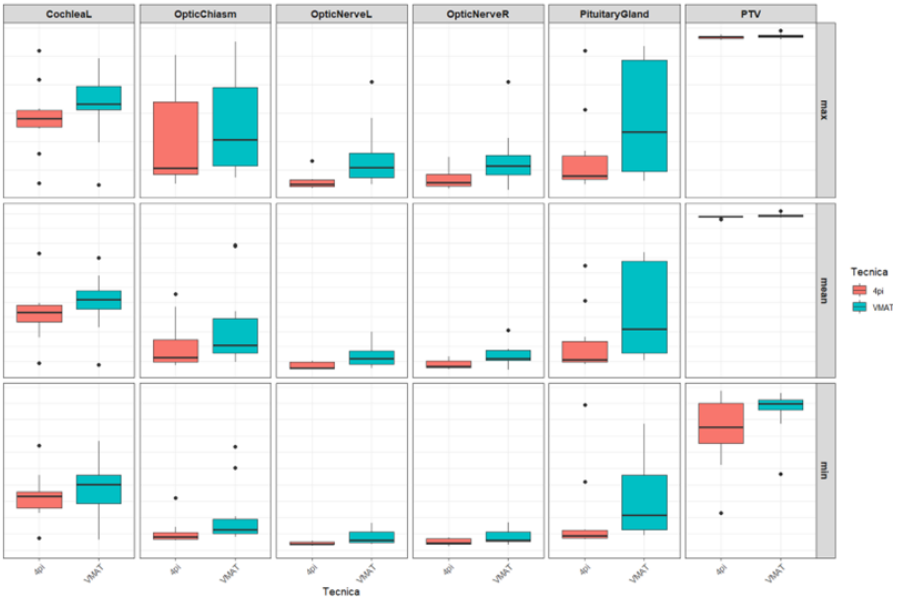


Figure 2: Percentage reduction in mean dose to OARs in the different techniques.



5.2 Homogeneity and Conformity of the Planning Target Volume (PTV)

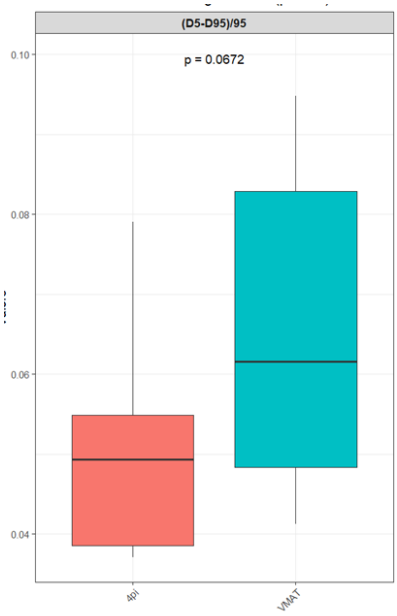
- The homogeneity index (HI), defined as $(D_5 - D_{95})/95$, was used to evaluate dose uniformity within the planning target volume (PTV). Lower HI values indicate more homogeneous dose distributions.

Structure	Mean (4π)	Mean (VMAT)	p-value
HI	0.050	0.066	0.067

The 4π plans demonstrated improved dose homogeneity compared to VMAT, with a lower mean HI. Although the difference did not reach statistical significance (p = 0.067), the trend suggests potential clinical relevance in reducing localized overdoses and improving tumor control. Therefore, it can be inferred that dose distribution is

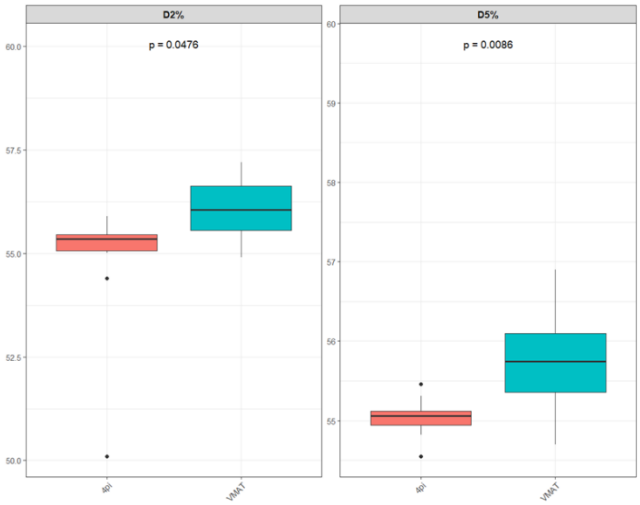
more homogeneous with the new non-coplanar technique, leading to better tumour control and fewer side effects thanks to the elimination of localised overdoses.

Figure 3: Pivot analysis of the Homogeneity Index.



Although the VMAT plans exhibited slightly higher near-maximum dose values compared to the 4π plans, the differences were modest yet statistically relevant. Specifically, the D2%, representing the dose received by the most irradiated 2% of the target volum, was 56.06 Gy for VMAT and 54.78 Gy for 4π, with a p-value of 0.05, indicating borderline statistical significance. Similarly, the D5% values were 55.77 Gy for VMAT and 55.04 Gy for 4π, with a p-value of 0.01, denoting a statistically significant difference. These findings suggest that VMAT plans tend to generate more pronounced dose peaks within the target volume, resulting in a less homogeneous dose distribution. In contrast, the 4π technique appears to better mitigate high-dose regions, promoting smoother dose gradients and potentially enhancing normal tissue sparing. This characteristic may be particularly advantageous in pediatric radiotherapy, where minimizing unnecessary exposure to surrounding healthy structures is critical.

Figure 4:



- The conformity index (CI), calculated as V_{RI}/PTV, assesses how well the prescribed dose conforms to the target volume. Values closer to 1 indicate optimal conformity.

Structure	Mean 4π	Mean VMAT	p-value
VRI/PTV	1,136	1,330	0,371

Both techniques yielded comparable conformity indices, with 4π showing slightly better confinement of dose to the target. However, the difference was not statistically significant (p = 0.371), suggesting similar performance in this metric within the analyzed cohort.

5.3 Integral Dose Analysis and Clinical Implications

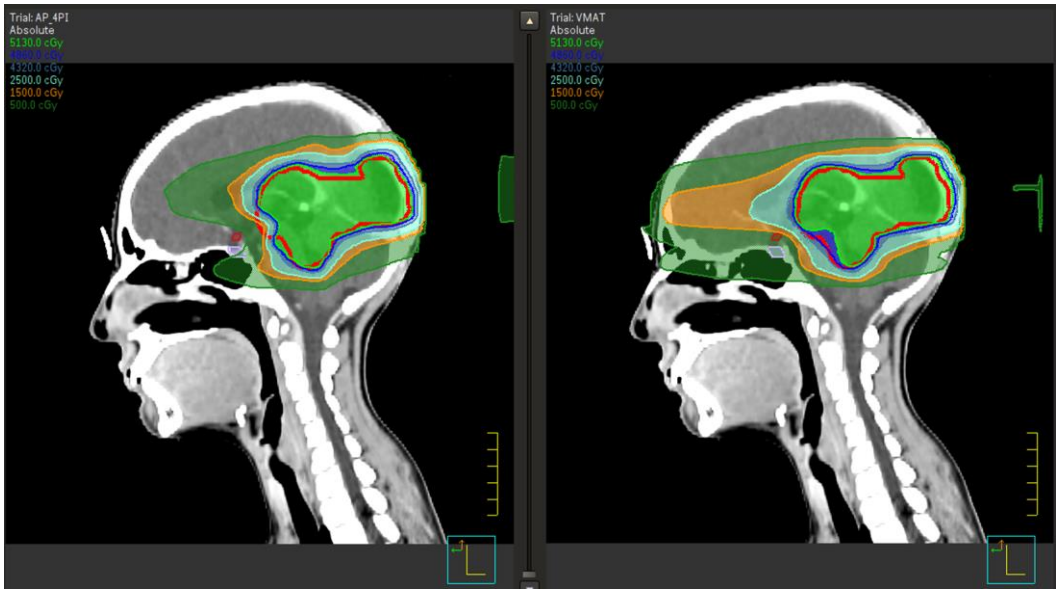
Integral dose, defined as the total energy deposited in non-target tissues, is a critical parameter linked to systemic toxicity and long-term risk of secondary malignancies.

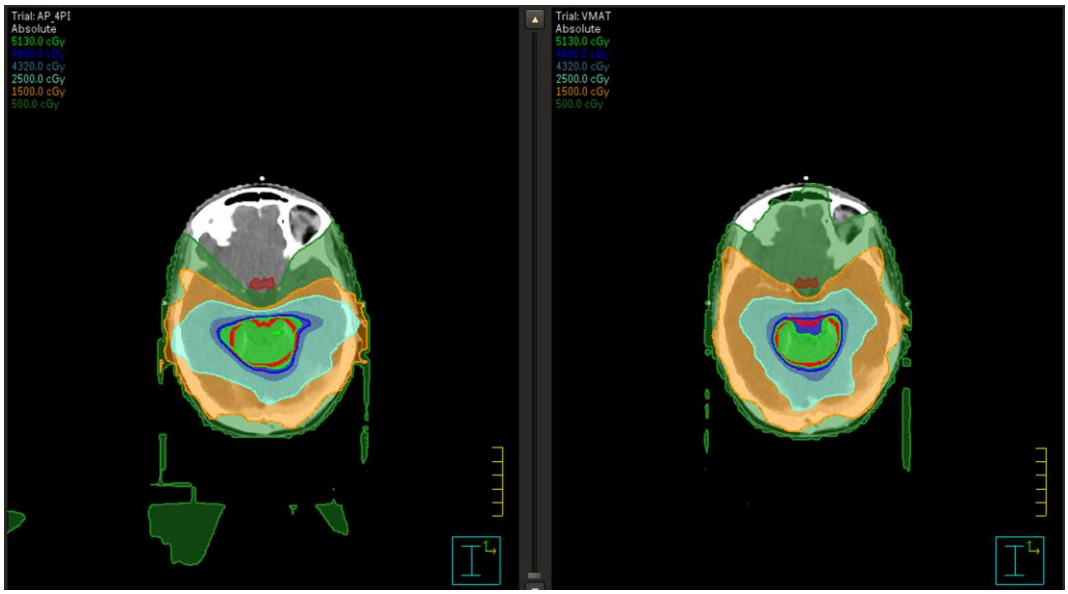
Structure	Mean (4π)	Mean (VMAT)	p-value
Integral Dose	7.836	8.517	0.493

The 4π technique resulted in a lower integral dose compared to VMAT, indicating reduced exposure of healthy tissues. Although the difference was not statistically significant (p = 0.493), this reduction may contribute to improved long-term safety profiles in pediatric patients.

The statistical analysis supports the potential dosimetric advantages of 4π radiotherapy in pediatric cranial irradiation. While some differences did not reach statistical significance, the observed trends favor improved homogeneity, reduced integral dose, and enhanced sparing of organs at risk.

Figure 5: comparison of dose distribution of treatment made with 4π radiotherapy versus conventional VMAT.




Trial: AP_4PI
Absolute
5130.0 cGy
4320.0 cGy
2500.0 cGy
1500.0 cGy
500.0 cGy
Trial: VMAT
Absolute
5130.0 cGy
4320.0 cGy
2500.0 cGy
1500.0 cGy
500.0 cGy

6. Discussion

6.1 Interpretation of Dosimetric Findings

6.2 Clinical Implications for Pediatric Radiotherapy

6.3 Comparison with Literature on CK and SRS

6.4 Study Limitations and Future Perspective

6. Discussion

6.1 Interpretation of Dosimetric Findings

The comparative dosimetric analysis between 4π and VMAT plans revealed consistent trends favoring the non-coplanar 4π technique across multiple metrics. Notably, the 4π plans demonstrated superior sparing of organs at risk (OARs), improved dose homogeneity within the planning target volume (PTV), and a reduction in integral dose.

The maximum dose to the left optic nerve was significantly lower in the 4π plan (4.895 Gy) compared to VMAT (9.125 Gy, $p = 0.0147$), with similar trends observed for the right optic nerve ($p = 0.0367$). These reductions are clinically meaningful, as high-dose exposure to optic structures is associated with increased risk of radiation-induced optic neuropathy, particularly in pediatric patients with longer life expectancy and heightened sensitivity to late effects.

The homogeneity index (HI) was lower in 4π plans (mean HI = 0.050) than in VMAT (mean HI = 0.066), suggesting a more uniform dose distribution. Although the difference did not reach statistical significance ($p = 0.067$), the trend aligns with prior studies indicating that non-coplanar beam arrangements can reduce dose heterogeneity and mitigate localized overdosing. This is further supported by the statistically significant reduction in D5% values (55.04 Gy vs. 55.77 Gy, $p = 0.01$), reinforcing the capacity of 4π planning to suppress high-dose peaks within the target volume.

The conformity index (CI) values were comparable between techniques (mean CI = 1.136 for 4π vs. 1.330 for VMAT, $p = 0.371$), indicating similar geometric coverage of the PTV. However, the slightly lower CI in 4π plans may reflect improved dose confinement, consistent with the enhanced angular modulation afforded by non-coplanar delivery.

Integral dose analysis revealed a modest reduction in total energy deposition to non-target tissues with 4π (7.836 vs. 8.517 Gy·L, $p = 0.493$). Although not statistically significant, this trend is relevant in pediatric radiotherapy, where minimizing integral dose is critical to reducing systemic toxicity and long-term risk of secondary malignancies.

6.2 Clinical Implications for Pediatric Radiotherapy

The dosimetric advantages observed with 4π planning have direct implications for pediatric neuro-oncology. Children are particularly vulnerable to radiation-induced damage due to ongoing neurodevelopment, increased radiosensitivity, and longer post-treatment survival. The significant reduction in optic nerve doses and the trend toward lower pituitary and brainstem exposure suggest that 4π radiotherapy may offer enhanced neuro-ocular and neuroendocrine protection.

Moreover, improved dose homogeneity within the PTV may contribute to better tumor control by ensuring consistent coverage while avoiding localized overdoses that could compromise adjacent healthy tissue. The reduction in integral dose further supports the use of 4π in pediatric settings, where long-term safety is paramount.

These findings align with current clinical priorities in pediatric radiotherapy, which emphasize precision, organ preservation, and minimization of late effects. The 4π technique, by leveraging non-coplanar beam geometry and advanced optimization algorithms, appears to fulfill these criteria more effectively than conventional VMAT.

6.3 Comparison with Literature on CK and SRS

The results of this study are consistent with published data on stereotactic modalities such as CyberKnife (CK) and stereotactic radiosurgery (SRS), which also employ non-coplanar beam arrangements to enhance conformity and reduce OAR exposure. Studies by Guckenberger et al. and Benedict et al. have demonstrated that CK achieves

superior dose gradients and sparing of critical structures in intracranial targets. Similarly, SRS techniques have shown improved homogeneity and reduced integral dose in small-volume pediatric tumors.

However, 4π planning differs from CK and SRS in its capacity to treat larger volumes with fractionated regimens, making it more suitable for complex pediatric cases requiring broader coverage and dose modulation. The present findings suggest that 4π may bridge the gap between conventional VMAT and stereotactic modalities, offering a hybrid solution that combines precision with scalability.

6.4 Study Limitations and Future Perspective

While the dosimetric trends observed in this study are promising, several limitations must be acknowledged. First, the sample size may limit statistical power, particularly in metrics such as CI and integral dose where differences did not reach significance. Second, the analysis was confined to planning data; clinical outcomes such as toxicity profiles, neurocognitive function, and endocrine sequelae were not assessed.

Future research should incorporate longitudinal follow-up to validate the clinical benefits of 4π planning in pediatric populations. Additionally, integration of biological modeling (e.g., NTCP, TCP) and adaptive planning strategies may further refine the therapeutic index. Comparative studies involving other advanced modalities such as proton therapy and MR-guided radiotherapy could also elucidate the relative advantages of 4π in specific clinical scenarios.

7. Conclusions

7.1 Summary of the Advantages of the 4π Technique

7.2 Recommendations for Future Clinical Studies

7.3 Ethical and Multidisciplinary Considerations

7. Conclusions

7.1 Summary of the Advantages of the 4π Technique

The comparative analysis between 4π and VMAT radiotherapy techniques in pediatric cranial irradiation highlights several advantages of the 4π approach. The non-coplanar beam geometry of 4π planning consistently demonstrated superior sparing of organs at risk (OARs), including statistically significant reductions in maximum and mean doses to critical structures such as the optic nerves and hypothalamic-pituitary axis. Additionally, the 4π technique yielded improved dose homogeneity within the planning target volume (PTV), as evidenced by lower homogeneity index (HI) values and reduced D2% and D5% metrics, suggesting a more uniform dose distribution and diminished risk of localized overdosing.

Although differences in conformity index (CI) and integral dose did not reach statistical significance, the observed trends favor 4π planning in terms of dose confinement and reduced energy deposition to non-target tissues. These dosimetric advantages are particularly relevant in pediatric neuro-oncology, where long-term toxicity, neurocognitive outcomes, and endocrine preservation are critical considerations.

7.2 Recommendations for Future Clinical Studies

While the present findings support the potential of 4π radiotherapy to enhance dosimetric quality and reduce exposure to healthy tissues, further clinical validation is warranted. Prospective studies should incorporate long-term follow-up to assess functional outcomes, late toxicity profiles, and quality of life in pediatric patients treated with 4π plans. Integration of biological modeling, including normal tissue complication probability (NTCP) and tumor control probability (TCP), may provide deeper insight into the therapeutic index of this technique.

Moreover, comparative trials involving other advanced modalities—such as proton therapy, MR-guided radiotherapy, and stereotactic systems like CyberKnife—could help delineate the optimal treatment strategy for specific tumor types and anatomical locations. Multicenter collaborations and standardized dosimetric protocols will be essential to ensure reproducibility and generalizability of results.

7.3 Ethical and Multidisciplinary Considerations

The implementation of advanced radiotherapy techniques in pediatric populations necessitates careful ethical and multidisciplinary evaluation. Treatment decisions should be guided not only by dosimetric superiority but also by considerations of accessibility, cost-effectiveness, and long-term survivorship. Involving pediatric oncologists, radiation oncologists, medical physicists, neuropsychologists, and patient advocates in the planning process ensures a holistic approach that prioritizes both oncologic control and functional preservation.

Given the heightened vulnerability of pediatric patients to radiation-induced sequelae, the adoption of techniques such as 4π radiotherapy must be accompanied by transparent communication with families, informed consent processes, and ongoing ethical oversight. Ultimately, the goal is to deliver precision therapy that maximizes efficacy while minimizing harm, in alignment with the principles of pediatric care and radiotherapeutic stewardship.