Regence

Medical Policy Manual Medicine, Policy No. 164

Intensity Modulated Radiotherapy (IMRT) of the Central Nervous System (CNS), Head, Neck, and Thyroid

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Last Review: November 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Intensity modulated radiotherapy (IMRT) is a form of radiation therapy that conforms closely to the targeted tumor shape and allows higher doses of radiation to be delivered while minimizing toxicity to surrounding healthy tissues.

MEDICAL POLICY CRITERIA

I. Intensity modulated radiotherapy (IMRT) of the head, neck, thyroid, and central nervous system may be considered **medically necessary** when any of the following criteria are met (NOTE: *This policy addresses specific indications only. Please see Medicine, Policy No. 167 for requests where only through IMRT can published dose/volume constraints be met for organs at risk*):

   A. There is documented prior radiation treatment to the planned target volume; or

   B. Definitive radiotherapy for pediatric (less than 21 years of age) central nervous system (CNS) tumors (Note: for palliative treatment of pediatric CNS and for the treatment of adult CNS with no prior radiation, see Medicine, Policy No. 167); or

C. Hippocampal-avoiding intensity-modulated radiotherapy for individuals with brain tumor metastases and both of the following:
    1. Metastases are outside a 5mm margin around the hippocampi; and
    2. Clinical documentation that expected survival is ≥4 months; or

D. For the treatment of head and neck cancers (Primary and recurrent cancers [excluding skin cancer] arising from the oral cavity and lip, larynx, hypopharynx, oropharynx, nasopharynx, paranasal sinuses and nasal cavity, salivary glands, and soft tissue sarcomas, unusual histologies or occult primaries in the head and neck region); or

E. For the treatment of lymphomas in the head and neck region, excluding follicular and malt and marginal zone lymphomas; or

F. For the treatment of thyroid cancer when any of the following criteria are met:
    1. Locoregional recurrence; or
    2. Anaplastic thyroid cancer; or
    3. Node positive or node-recurrent; or
    4. There is documentation of muscle invasion.

II. Intensity-modulated radiotherapy (IMRT) is considered **not medically necessary** for the treatment of tumors of the head, neck, thyroid, and central nervous system not meeting Criterion I. above (NOTE: *Please use Medicine, Policy No. 167 for requests where only through IMRT can published dose/volume constraints be met for organs at risk*).

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

ORGANS AT RISK

Organs at risk are defined as normal tissues whose radiation sensitivity may significantly influence treatment planning and/or prescribed radiation dose. These organs at risk may be particularly vulnerable to clinically important complications from radiation toxicity. At-risk organs may include temporal lobe, hippocampus, brain stem, spinal cord, cochlea and eye structures including optic nerve and chiasm, lens, retina and lacrimal gland.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome. Quality assurance for 3D and IMRT submitted plans are not required with a preauthorization request.

- Clinical history
- Physical/chart notes

- Relevant imaging reports documenting that the policy criteria are met for medical necessity.
- For hippocampal-avoiding intensity-modulated radiotherapy for individuals with brain tumor metastases, documentation of expected survival

CROSS REFERENCES

1. Charged-Particle (Proton) Radiotherapy, Medicine, Policy No. 49
2. Intensity Modulated Radiotherapy (IMRT) of the Thorax, Abdomen, Pelvis, and Extremities, Medicine, Policy No. 165
3. Intensity Modulated Radiotherapy (IMRT) for Breast Cancer, Medicine, Policy No. 166
4. Intensity Modulated Radiotherapy (IMRT) for Tumors in Close Proximity to Organs at Risk, Medicine, Policy No. 167
5. Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy for Intracranial, Skull Base, and Orbital Sites, Surgery, Policy No. 213
6. Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy for Tumors Outside of Intracranial, Skull Base, or Orbital Sites, Surgery, Policy No. 214

BACKGROUND

RADIATION TECHNIQUES

Conventional External Beam Radiotherapy

Over the past several decades, methods to plan and deliver RT have evolved in ways that permit more precise targeting of tumors with complex geometries. Most early trials used two-dimensional treatment planning based on flat images and radiation beams with cross-sections of uniform intensity that were sequentially aimed at the tumor along two or three intersecting axes. Collectively, these methods are termed “conventional external beam RT.”

Three-Dimensional Conformal Radiotherapy

Treatment planning evolved by using three-dimensional images, usually from computed tomography (CT) scans, to delineate the boundaries of the tumor and discriminate tumor tissue from adjacent normal tissue and nearby organs at risk for radiation damage. Computer algorithms were developed to estimate cumulative radiation dose delivered to each volume of interest by summing the contribution from each shaped beam. Methods also were developed to position the patient and the radiation portal reproducibly for each fraction and immobilize the patient, thus maintaining consistent beam axes across treatment sessions. Collectively, these methods are termed three-dimensional conformal radiotherapy (3D-CRT).

Intensity-Modulated Radiotherapy

IMRT, which uses computer software and CT and magnetic resonance imaging (MRI) images, offers better conformality than 3D-CRT, as it is able to modulate the intensity of the overlapping radiation beams projected on the target and to use multiple shaped treatment fields. It uses a device (a multileaf collimator [MLC]) which, coupled to a computer algorithm, allows for “inverse” treatment planning. The radiation oncologist delineates the target on each slice of a CT scan and specifies the target’s prescribed radiation dose, acceptable limits of dose heterogeneity within the target volume, adjacent normal tissue volumes to avoid, and acceptable dose limits within the normal tissues. Based on these parameters and a digitally reconstructed radiographic image of the tumor and surrounding tissues and organs at risk,

computer software optimizes the location, shape and intensities of the beams ports, to achieve the treatment plan's goals.

Increased conformality may permit escalated tumor doses without increasing normal tissue toxicity and thus may improve local tumor control, with decreased exposure to surrounding, normal tissues, potentially reducing acute and late radiation toxicities. Better dose homogeneity within the target may also improve local tumor control by avoiding underdosing within the tumor and may decrease toxicity by avoiding overdosing.
Because most tumors move as patients breathe, dosimetry with stationary targets may not accurately reflect doses delivered within target volumes and adjacent tissues in patients. Furthermore, treatment planning and delivery are more complex, time consuming, and labor intensive for IMRT than for 3D-CRT. Thus, clinical studies must test whether IMRT improves tumor control or reduces acute and late toxicities when compared with 3D-CRT.

BRAIN TUMORS

The standard approach to the treatment of brain tumors depends on the type and location of tumor. For glioblastoma multiforme, a malignant high-grade tumor, treatment is multimodal, with surgical resection followed by adjuvant radiotherapy (RT) and chemotherapy.[1]

For benign and low-grade brain tumors, gross total resection remains the primary goal. However, RT may be used in selected cases. Some examples are when total resection is not possible, when a more conservative surgical approach may be necessary to achieve long-term treatment goals, and with atypical tumors that may need RT even after gross total resection to reduce the risk of local recurrence. Therefore, RT, either definitive or in the postoperative adjuvant setting, remains an integral component in the management of residual, recurrent, and/or progressive benign and low-grade brain tumors for maximizing local control.[2]

Brain metastases occur in up to 40% of adults with cancer and can shorten survival and detract from quality of life. Many patients who develop brain metastases will eventually die of progressive intracranial disease. Among patients with good performance status, controlled extracranial disease, favorable prognostic features, and a solitary brain metastasis, randomized studies have shown that surgical excision followed by whole-brain radiotherapy (WBRT) or stereotactic radiotherapy to the post resection cavity prolongs survival.[3]
Stereotactic radiosurgery (SRS) may be able to replace surgery in certain circumstances, delivering obliteratively high single doses to discrete metastases. For bulky cerebral metastases, level one evidence has also shown that delivering a higher radiation dose with an SRS boost is beneficial in addition to standard WBRT. The use of a concomitant boost with IMRT during WBRT has been attempted to improve overall local tumor control without the use of SRS to avoid additional planned radiation after WBRT ("phase II" or SRS) and its additional labor and expense.[3]

HEAD AND NECK TUMORS

Head and neck cancers account for approximately 3% to 5% of cancer cases in the United States. The generally accepted definition of head and neck cancers includes cancers arising from the oral cavity and lip, larynx, hypopharynx, oropharynx, nasopharynx, paranasal sinuses and nasal cavity, salivary glands, and occult primaries in the head and neck region. Cancers generally not considered as head and neck cancers include uveal and choroidal melanoma, cutaneous tumors of the head and neck, esophageal cancer, and tracheal cancer. Thyroid cancers are also addressed in this policy. EBRT is uncommonly used in the treatment of

thyroid cancers but may be considered in patients with anaplastic thyroid cancer and for locoregional control in patients with incompletely resected high-risk or recurrent differentiated (papillary, follicular, or mixed papillary-follicular) thyroid cancer.

EVIDENCE SUMMARY

Multiple-dose planning studies have generated 3D-CRT and intensity-modulated radiotherapy (IMRT) treatment plans from the same scans, then compared predicted dose distributions within the target and in adjacent organs at risk. Results of such planning studies show that IMRT improves on 3D-CRT with respect to conformality to, and dose homogeneity within, the target. Dosimetry using stationary targets generally confirms these predictions. Thus, radiation oncologists hypothesized that IMRT may improve treatment outcomes compared with those of 3D-CRT. However, these types of studies offer indirect evidence on treatment benefit from IMRT, and it is difficult to relate results of dosing studies to actual effects on health outcomes.

Comparative studies of radiation-induced side effects from IMRT versus alternative radiation delivery are probably the most important type of evidence in establishing the benefit of IMRT. Such studies would answer the question of whether the theoretical benefit of IMRT in sparing normal tissue translates into real health outcomes. Single-arm series of IMRT can give some insights into the potential for benefit, particularly if an adverse effect that is expected to occur at high rates is shown to decrease by a large amount. Studies of treatment benefit are also important to establish that IMRT is at least as good as other types of delivery.

Evidence from randomized controlled trials comparing IMRT with other radiation techniques is needed in order to establish safety (e.g., toxicity) and efficacy (i.e., impact on clinical outcomes such as survival) of IMRT in the treatment of tumors of the central nervous system (CNS).

The available evidence on IMRT for treatment of tumors of CNS comes from observational studies (retrospective comparisons, single arm studies) with methodological limitations such as small sample sizes and heterogenous study populations. A significant number of the available studies are dose planing reports. Only a limited number of studies address clinical outcomes (e.g., overall survival, tumor control). These studies report inconsistent findings. However, the available studies consistently report better sparing of healthy tissues and reduced toxicity in IMRT-treated patients.

HIGH-GRADE MALIGNANT CNS TUMORS

Systematic Reviews

Amelio (2010) conducted a systematic review on the clinical and technical issues of using IMRT in newly diagnosed glioblastoma multiforme (GBM).[4] The articles included in the review were through December 2009 and included 17 studies (nine related to dosimetric data and technical considerations, seven to clinical results, and one to both dosimetric and clinical results) for a total of 204 treated patients and 148 patient datasets used in planning studies. No randomized controlled studies (RCTs) were identified, and a meta-analysis was not performed.

For the six papers related to planning studies that compared either 3D-CRT versus IMRT, one study showed a noticeable difference between 3D-CRT and IMRT for the planning target volume (PTV) (13% benefit in V95 [volume that received 95% of the prescribed dose] from IMRT, $p<0.001$)[5]; the remaining studies suggested that IMRT and 3D-CRT provide similar

PTV coverage, with differences between 0 and 1%. Target dose conformity was found to be improved with IMRT.

The organs at risk (OAR) typically under consideration in the studies were the brainstem, optic chiasm, optic nerves, lens and retina. In general, IMRT allowed better sparing of the OAR than 3D-CRT but with considerable variation from study to study.

The eight studies that included clinical results included three retrospective, one prospective Phase I and IV prospective Phase II single institution studies. Of these eight studies, two used conventional total dose and dose per fraction, two used a hypofractionated regimen, and in the remaining, a hypofractionated scheme using a simultaneous integrated boost. Chemotherapy was administered in six of eight series, concomitantly with radiation and in the adjuvant phase. Median follow-up ranged from 8.8 and 24 months. Almost all patients (96%) were able to complete the treatment without interruption/discontinuation due to toxicity. Acute toxicity was reported as negligible with grade-3 side effects observed in only two studies at rates of 7% and 12%. Grade-4 toxicity was recorded in only one series with an absolute rate of 3%. Data for late toxicities were available in 6/8 studies, with one study recording grade 4 side effects with an incidence of 20%. One-year and two-year overall survival (OS) varied between 30% and 81.9% and between 0% and 55.6%, respectively. When OS was reported as a median time, its value ranged from 7 to 24 months. Progression-free survival (PFS) ranged from 0% and 71.4% at one year and 0% and 53.6% at two years. Median PFS was reported as ranging from 2.5 to 12 months.

The authors also carried out a comprehensive qualitative comparison with data reported in the literature on similar non-IMRT clinical studies and offered the following conclusions. The results of the planning comparisons showed 3D-CRT and IMRT techniques provide similar results in terms of target coverage, IMRT is somewhat better than 3D-CRT in reducing the maximum dose to the OAR, although the extent varied from case to case, IMRT is clearly better than 3D-CRT in terms of dose conformity and sparing of the healthy brain at medium to low doses and that (in general) there were no aspects where IMRT seemed worse than 3D-CRT.

This evidence is limited by a number of factors. There is an absence of comparative studies with clinical outcomes, all of the studies were small in size, from a single institution, a majority of patients (53%) were retrospectively analyzed, and the administration of chemotherapy was variable across studies.

Nonrandomized Studies

A representative sample of nonrandomized comparative studies and single-arm studies with clinical outcomes are discussed below.

Bao (2020) reported a retrospective analysis of patients with esthesioneuroblastoma who were treated with IMRT.[6] Of the 52 total patients, 44 were newly diagnosed and 8 had recurrent disease. Fifteen patients had regional lymph node metastasis. Median follow-up was 32.5 months. Three-year OS, progression-free survival, regional progression-free survival, and distant metastasis-free survival rates were 89.7, 69.5, 89.7, 95.1, and 85.4%, respectively. According to a multivariate analysis, the only significant prognostic factor for any survival outcome was the presence of nodal disease, which was a prognosticator for progression-free survival. No grade 3 or 4 IMRT-induced acute toxicities were reported. Severe late toxicities

were 11.5% overall, 3.8% for dysosmia, 3.8% for hearing loss, 1.9% for radiation brain injury, and 1.9% for temporal lobe necrosis. No late ocular toxicity secondary to IMRT was reported.

A large cohort study conducted by Xiang (2020) that included >450,000 patients with cancer (of which 12,143 had brain or central nervous system cancer) compared the risk of secondary tumors following treatment with IMRT and 3D-CRT across cancer types.[7] After a mean five years follow-up, multivariate, matched analysis showed no difference in risk of secondary cancers between IMRT and 3D-CRT (OR 1.00, 95% CI 0.98 to 1.03). These results were consistent when limited to patients who had not received chemotherapy (OR 1.01, 95% CI 0.96 to 1.06).

Byun (2019) assessed predictors of acute severe lymphopenia (ASL) in glioblastoma patients treated with radiation therapy plus immunotherapy.[8] Radiation therapy was delivered by 3D-CRT in 186 patients and IMRT in 150 patients. IMRT was independently associated with decreased ASL incidence (HR, 0.48; 95% CI, 0.27-0.87; p=0.015) and according to a propensity-matched comparison, the incidence of ASL was lower with IMRT than with 3D-CRT (20% vs. 37%; p=0.005). In addition, a multivariable analysis indicated that increased planned target volume was independently associated with increased ASL incidence (HR, 1.02; 95% CI 1.00 to 1.03; p=0.042). Patients with ASL had significantly worse overall survival than those without at a median follow-up of 19.3 months (median, 18.2 vs. 22.0 months; p=0.028).

Paulsson (2014) compared treatment failure rates in GBM patients treated with IMRT or 3D conformal RT with differing target margins (the size of the region between tumor and edge of the planning target volume).[9] This comparison indirectly evaluated IMRT and older techniques, because the use of IMRT has been accompanied by changes in treatment planning. In 161 patients, treatment margins were not associated with treatment failure. There was no difference in treatment failure between IMRT and 3D-CRT.

Chen (2013) assessed whether IMRT improved clinical outcomes compared with 3D-CRT in patients with GBM in a retrospective study of 54 patients.[10] The median follow-up was 13 months. Of the 54 patients, 50 (92.6%) completed the combined modality treatment (patients underwent postoperative IMRT or 3D-CRT with concurrent and adjuvant temozolomide). The one-year overall survival rate (OS) was 79.6%. The pattern of failure was predominantly local. A comparative analysis revealed that no statistical difference was observed between the IMRT group (n=21) and the 3D-CRT group (n=33) for one-year OS (89.6% vs. 75.8%, p=0.795), or one-year progression-free survival (PFS) (61.0% vs. 45.5%, p=p 0.867). In dosimetric comparison, IMRT seemed to allow better sparing of organs at risk than 3D-CRT (p==0.050, p=0.055). However, there was no significant difference for toxicities of irradiation between the IMRT group and the 3D-CRT group. The authors concluded that preliminary results suggest that delivering standard radiation doses by IMRT is unlikely to improve local control or overall survival for GBM compared with 3D-CRT.

MacDonald (2007) compared the dosimetry of IMRT and 3D-CRT in 20 patients treated for high-grade glioma.[11] Prescription dose and normal-tissue constraints were identical for the 3D-CRT and IMRT treatment plans. The IMRT plan yielded superior target coverage as compared with the 3D-CRT plan. The IMRT plan reduced the percent volume of brainstem receiving a dose greater than 45 Gy by 31% (p=0.004) and the percent volume of brain receiving a dose greater than 18 Gy, 24 Gy, and 45 Gy by 10% (p=0.059), 14% (p=0.015), and 40% (p≤=0.0001), respectively. With IMRT, the percent volume of optic chiasm receiving more than 45 Gy was reduced by 30.4% (p=0.047). As compared with 3D-CRT, IMRT significantly

increased the tumor control probability (p≤0.0005) and lowered the normal-tissue complication probability for brain and brain stem (p<0.033).

Narayana (2006) reported the outcomes of 58 consecutive patients with high-grade gliomas treated with IMRT.[12] GBM accounted for 70% of cases and anaplastic gliomas for the remainder. Surgery consisted of biopsy alone in 26% of patients and of those that underwent resection, 63% had total or near total resection and 37% had partial resection. Eighty percent of patients received adjuvant chemotherapy. Median follow-up was 24 months. Acute neurotoxicities were grade 1 or 2 in 36% of patients, grade 3 in 7%, and grade 4 in 3%. Late toxicities were grade 1 or 2 in 10%, grade 3 in 7%, and no grade four or five. Freedom from late neurotoxicity at 24 months was 85%. Median OS for the anaplastic astrocytomas was 36 months and nine months for the GBM group. From these data, the authors concluded that the use of IMRT in high-grade gliomas does not appear to improve survival

Narayana (2006)[12] also performed a comparison of the IMRT treatment plans with 3D plans performed in 20 patients out of 58 total in that case series. Regardless of tumor location, IMRT did not improve PTV target coverage compared to 3D planning. IMRT decreased the maximum dose to the spinal cord, optic nerves, and eye by 16%, 7%, and 15%, respectively. These data indicate that IMRT may result in decreased late toxicities.

Huang (2002) compared ototoxicity with use of conventional (2D) radiotherapy (n=11) versus IMRT (n=15) in 26 pediatric patients with medulloblastoma.[13] All of the patients also received chemotherapy. When compared to conventional radiotherapy, IMRT delivered 68% of the radiation dose to the auditory apparatus, but full doses to the desired target volume. Median follow-up for audiometric evaluation was 51 months (9 to 107 months) for the conventional radiotherapy group and 18 months (8 to 37 months) for the group that received IMRT. Thirteen percent of the IMRT group had grade 3 or 4 hearing loss, compared to 64% of the conventional radiotherapy group (p<0.014).

Section Summary

Dosimetry studies have demonstrated lower radiation exposure to organs at risk with IMRT treatment plans compared with 3D-CRT treatment plans. Limited comparative evidence has shown lower rates of hearing loss with IMRT than with conventional radiotherapy. The evidence appears to be consistent in supporting lower neurotoxicity associated with IMRT. No conclusions can be made about comparative efficacy.

BENIGN CNS TUMORS

Rogers (2020) published a case series that included 57 patients with new or recurrent meningioma (WHO Grade 2 or 3) treated with 60 Gy high dose and 54 Gy low dose IMRT following resection.[14] Three-year PFS was 58.8% and overall survival at a mean followup of four years was 78.6%. Serious adverse events were rare (1.9%).

Reddy (2012) published a prospective phase II trial (n=24) of patients with newly diagnosed glioblastoma multiforme treated with hypofractionated IMRT with concurrent adjuvant temozolomide.[15] After a median follow-up of 14 months, there were no grade 3 or higher nonhematologic toxicities and the median overall survival was 16.6 months. There were six patients with suspected recurrence. The authors concluded that treatment was comparable to current standards of care.

Milker-Zabel (2007) reported the results of the treatment of complex-shaped meningiomas of the skull base with IMRT in 94 patients.[16] Patients received radiotherapy as primary treatment (n=26) postoperatively for residual disease (n=14) or after local recurrence (n=54). Tumor histology was World Health Organization grade 1 in 54.3%, grade two in 9.6%, and grade 3 in 4.2%. Median follow-up was 4.4%. Overall local tumor control was 93.6%. Sixty-nine patients had stable disease (by computed tomography [CT]/magnetic resonance imaging [MRI]), and 19 had a tumor volume reduction after IMRT. Six patients had local tumor progression on MRI a median of 22.3 months after IMRT. In 39.8% of patients, preexisting neurologic deficits improved. Treatment-induced loss of vision was seen in one of 53 re-irradiated patients with a grade 3 meningioma nine months after retreatment with IMRT.

Mackley (2007) reported outcomes of treating pituitary adenomas with IMRT.[17] A retrospective chart review was conducted on 34 patients treated between 1998 and 2003 at the Cleveland Clinic. Median follow-up was 42.5 months. Radiographic local control was 89%, and among patients with secretory tumors, 100% had a biochemical response. One patient required salvage surgery for progressive disease, resulting in a clinical PFS of 97%. One patient who received more than 46 Gy experienced optic neuropathy eight months after radiation.

Sajja (2002) reported the outcomes of 35 patients with 37 meningiomas treated with IMRT.[18] Tumor histology was benign in 35 and atypical in two tumors. The median CT/MRI follow-up was 19.1 months (range 6.4 to 62.4 months). Fifty-four percent of the meningiomas had been previously treated with surgery/radiosurgery prior to IMRT, and 46% were treated with IMRT, primarily after a diagnosis was established by CT/MRI. Three patients had local failure after treatment. No long-term complications from IMRT were documented among the 35 patients.

Uy (2002) assessed the safety and efficacy of IMRT in the treatment of intracranial meningioma in 40 patients treated between 1994 and 1999.[19] Twenty-five patients received IMRT after surgery either as adjuvant therapy for incomplete resection or for recurrence, and 15 patients received definitive IMRT after a presumptive diagnosis of meningioma on imaging. Thirty-two patients had skull base lesions and eight had nonskull base lesions. Follow-up ranged from 6 to 71 months (median 30 months). Defined normal structures generally received a significantly lower dose than the target. The most common acute CNS toxicity was mild headache, usually relieved with steroids. One patient experienced Radiation Therapy Oncology Group (RTOG) Grade 3 acute CNS toxicity, and two experienced Grade 3 or higher late CNS toxicity, with one possible treatment-related death. No toxicity was observed with mean doses to the optic nerve/chiasm up to 47 Gy and maximum doses up to 55 Gy. Cumulative five-year local control, PFS, and OS were 93%, 88%, and 89%, respectively.

Section Summary

The evidence on IMRT for the treatment of benign brain tumors includes noncomparative trials and case series. Results are consistent with low radiation toxicity but have not demonstrated better tumor control or improved survival with IMRT vs other radiotherapy techniques. The dose-planning studies evaluating IMRT in patients with malignant tumors should generalize to patients with benign brain tumors because the benefit of minimizing radiation toxicity to sensitive brain areas is identical.

BRAIN METASTASES

In 2021, Yang published a phase II RCT of patients with brain metastases treated with WBRT with or without hippocampal sparing.[20] To allow blinding of patients, all patients were treated with VMAT, which resulted in a similar treatment experience for both treatment groups. The health professionals who assessed neurocognitive functions were also blinded. The primary endpoint was decline of the Hopkins Verbal Learning Test-Revised (HVLT-R) delayed recall at four months post-treatment. This study was conducted in Taiwan and all tests and questionnaires used were Traditional Mandarin versions. Of the 70 patients randomized, 35 were assigned to the hippocampal sparing group (33 completed treatment and 24 had at least four months of follow-up) and 35 were assigned to the no-hippocampal sparing group (32 completed treatment and 24 had at least four months of follow-up). There was no baseline difference in neurocognitive function between the groups. Median follow-up was 12.4 months. There was no significant difference between groups in the primary outcome of HVLT-R delayed recall at four months (-8.8% for hippocampal sparing vs +3.8% without sparing; p=0.31). There were also no differences in brain PFS or OS between groups. At six months post-treatment, patients with hippocampal sparing had significantly better preservation of the HVLT-R recognition-discrimination index (mean difference = 1.78, p=0.019) and memory score (mean difference = 4.38, p=0.020) compared with patients without hippocampal sparing. There was no significant difference between groups at this time point for HVLT-R total recall (mean difference = 2.60, p=0.079).

Brown (2020) reported results from a phase III trial of 518 patients with brain metastases that assessed the comparative effectiveness of hippocampal-avoiding WBRT (HA-WBRT) using IMRT with conventional WBRT; both groups received memantine.[21] Study inclusion criteria required that patients have no brain metastases outside a 5-mm margin around either hippocampus. The primary outcome was time to loss of cognitive function, though OS and toxicity were also reported. After a mean eight-months follow-up, HA-WBRT was associated with a reduced loss of cognitive function (adjusted HR 0.74, 95% CI 0.58 to 0.95) without any difference between groups in overall survival (HR, 1.13, 95% CI 0.90 to 1.41). Specifically, at the four-month follow-up, the HA-WBRT showed less loss of executive function (23.3% v 40.4%; p=0.01), while at six months, there was less decline in learning (11.5% v 24.7%, p= 0.049) and memory (16.4% vs. 33.3%, p=0.02) in the HA-WBRT group. At six months, patients in the HA-WBRT plus memantine arm reported less difficulty with remembering things (mean, 0.16 v 1.29; p=0.01) and less difficulty speaking (mean 20.20 v 0.45; p=0.049) compared with the WBRT plus memantine arm. There was no difference between groups in quality of life at any time point, nor was there a difference between groups in grade 3 or higher toxicity. The study authors noted that the treatment was likely to be most effective in patients with more than four months expected survival, due to cognitive deterioration likely to occur in those with shorter expected survival. This trial indicates evidence of benefit of HA-WBRT versus WBRT on cognitive outcomes (absolute risk difference 10%) and there were no differences in toxicity, intracranial PFS, or OS.

Limitations of this study include that at the four-month follow-up, only about half of the enrolled participants in both groups provided data for the individual cognitive assessments, because a large proportion of the participants had died. This was also the time point at which a clear difference emerged between groups showing a lower risk of cognitive failure in the HA-WBRT group. In addition, a significantly higher proportion of those allocated to HA-WBRT did not receive treatment 10.7% (28/261) compared to 3.1% (8/257) in the WBRT group (p=0.0016).

Westover (2020) reported results of a single-institution noncomparative study of IMRT used to deliver hippocampal-sparing whole brain irradiation with simultaneous integrated boost (SIB)

for patients with brain metastases.[22] The median age of the 50 included patients was 60 years (interquartile range 54 to 65). Median progression-free and overall survival were 2.9 months (95% CI 1.5 to 4.0) and nine months, respectively. There was a high exclusion rate from cognitive testing due to disease-related factors. Three months post-WBRT, for those who completed testing, the mean decline in Hopkins Verbal Learning Test-Revised delayed was 10.6% (95% CI -36.5% to 15.3%). With death as a competing risk, one-year cumulative incidence of local and intracranial failure were 8.8% (95% CI 2.7% to 19.6%) and 21.3% (95% CI 10.7% to 34.2%), respectively. Three patients experienced grade 3 toxicities. No statistically significant change in Multidimensional Fatigue Inventory (MFI)-20 scores was reported at three months.

Du (2020) retrospectively evaluated the OS of patients who underwent radiotherapy for lung cancer brain metastases.[23] Of the 144 patients enrolled, 77 received WBRT, 39 received WBRT with consecutive boost, and 28 received SIB-IMRT. The longest OS was reported in the SIB-IMRT group, and the differences between the SIB-IMRT group and both the WBRT with consecutive boost group and the WBRT group were statistically significant (SIB-WBRT: median OS 14 months; 95% CI 8.8 to 19.1; WBRT: median OS 7 months; 95% CI 5.5 to 8.5 months, log-rank $p<0.001$; WBRT + boost group: median OS 11; 95% CI 8.3 to 13.7 months, log-rank $p=0.037$). Multivariable analyses showed that the decrease in mortality risk in SIB-IMRT-treated patients ranged from 56% to 64%, depending on the model used (for all $p<0.001$).

Gondi (2014) evaluated IMRT as a method to avoid radiation exposure to the hippocampus and prevent adverse cognitive events in patients receiving WBRT.[24] The Gondi study was a prospective trial with a prespecified comparison to a historical control group derived from a previously conducted clinical trial. The outcomes were standardized cognitive assessments, and health-related quality of life evaluated at baseline and two-month intervals (out to six months).

Of 100 eligible patients, 42 patients were evaluable at four months; 17 patients were alive but did not have cognitive testing, and 41 had died. The mean decline in the primary cognitive endpoint was 7.0%, which was significantly less than the 30% decline in the historical control group ($p<0.001$). Median survival in the experimental group was 6.8 months and 4.9 months in the historical control group. Although the trial results suggested that hippocampal-sparing WBRT using IMRT is associated with less cognitive decline, the historical control design adds uncertainty to the conclusion. Because the experimental group had survived longer, even though the radiation dose was intended to be equivalent to the historical control, possible unmeasured patient factors associated with better survival may have also caused less cognitive decline. The trial did not provide conclusive evidence that hippocampal-sparing IMRT causes less cognitive decline.

A retrospective study, published by Zhou in 2014, was designed to evaluate the feasibility of WBRT plus simultaneous integrated boost (SIB) with IMRT for inoperable brain metastases of NSCLC.[25] Twenty-nine NSCLC patients with 87 inoperable brain metastases were included. All patients received WBRT at a dose of 40 Gy and SIB boost with IMRT at a dose of 20 Gy concurrent with WBRT in the fourth week. Prior to each fraction of image-guided (IG) IMRT boost, on-line positioning verification and correction were used to ensure that the set-up errors were within 2 mm by cone beam CT in all patients. The one-year intracranial control rate (ICR), local brain failure rate (BFR), and distant BFR were 63%, 14%, and 19%, respectively. The two-year ICR, local BFR, and distant BFR were 42%, 31%, and 36%, respectively. Both

median intracranial PFS and median OS were 10 months. Six-month, one-year, and two-year OS rates were 66%, 41%, and 14%. Patients with Score Index for Radiosurgery in Brain Metastases (SIR) greater than five, number of intracranial lesions less than three and history of epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR-TKI) treatment had better survival. Radiation necrosis was observed in three (3.5%) lesions after radiotherapy. Grades 2 and 3 cognitive impairment with grade two radiation leukoencephalopathy were observed in four (14%) and four (14%) patients. No dosimetric parameters were found to be associated with these late toxicities. Patients who received EGFR-TKI treatment had higher incidence of grades 2 to 3 cognitive impairment with grade 2 leukoencephalopathy. This evidence suggests WBRT plus SIB with IMRT is a tolerable treatment for NSCLC patients with inoperable brain metastases. However, the evidence does not allow conclusions as to its efficacy.

Edwards (2010) reported outcomes on the use of whole brain radiotherapy (WBRT) with an IMRT boost in 11 patients with metastatic disease to the brain ranging from 25 to 80 mm in maximum diameter.[26] Patients were excluded if they had more than four metastases. Histologies of the metastases included primary lung (n=5), breast (n=4), colon (n=1), and kidney (n=1). There were no acute or subacute complications. All tumors showed response on a one-month post-radiotherapy scan. Median follow-up was four months. Four of the 11 patients died of systemic disease six to nine months after radiotherapy. The remaining patients were alive with no evidence of progression of the treated brain disease or local recurrence at two to nine months after radiotherapy. No brain complications occurred to date.

HEAD AND NECK CANCERS

Systematic Reviews and Technology Assessments

Razavian (2023) published a systematic review and meta-analysis to assess local failure (LF) and regional failure (RF) after IMRT for early glottic laryngeal cancer.[27] Fifteen studies involving 2083 patients were included. Fourteen studies were retrospective and median follow-up times ranged from 18 to 66 months. The crude LF rate after IMRT was 7.6% (n=795) and the RF was 1.5%. Conventional radiation therapy (CRT) was associated with a crude RF rate of 12.2% and RF of 1.9% (n=738). The authors concluded the outcomes from IMRT compared to CRT are similar but the analysis was limited by the use of a small subset of studies for analysis of LF and RF rates, and heterogeneity of treatment methods.

Ge (2020) recently evaluated the effects of IMRT as compared to conventional RT with regard to quality of life and xerostomia severity in 761 patients with head and neck cancer.[28] This meta-analysis included data from seven studies: three RCTs, two prospective studies, one prospective case control study, and one retrospective study. Overall, patients who underwent IMRT had a better global health status (pooled standardized mean difference [SMD], 0.80; 95% CI 0.26 to 1.35; p=0.004) and improved cognitive function (pooled SMD, 0.30; 95% CI 0.06 to 0.54; p=0.013) as compared to patients who underwent conventional RT. Intensity-modulated radiotherapy was also associated with significantly lower scores for xerostomia than conventional RT (pooled SMD, -0.60; 95% CI -0.97 to -0.24; p=0.001). There were no differences between the groups with regard to emotional function (p=0.531) and social function (p=0.348). The analysis was limited by a small number of included studies, heterogeneity of data, and relatively small sample sizes.

Lee (2020) published results of a meta-analysis of IMRT reirradiation for recurrent or secondary head and neck cancer.[29] Of the seventeen studies that met inclusion criteria

(n=1635), 14 were retrospective and 15 were from a single institution. Pooled two-year LC and OS rates were 52% (95% CI 46% to 57%) and 46% (95% CI 41% to 50%), respectively. Pooled late grade ≥ 3 and grade 5 toxicity rates were 26% (95% CI 20% to 32%) and 3.1% (95% CI 2% to 5%), respectively.

Alterio (2020) performed a systematic review and meta-analysis to assess the toxicity and oncological outcomes of IMRT and 2D/3D RT for oropharyngeal cancer.[30] A total of eight studies met inclusion criteria, six of which were included in the meta-analysis. Frequencies of acute and late toxicities were higher in the 2D/3D RT group. No statistically significant differences between groups were identified for death (SRR=0.93, 95% CI 0.83 to 1.04, with no heterogeneity I^2=0%) or relapse (SRR= 0.92, 95% CI 0.83 to 1.03, with no heterogeneity I^2=0%).

De Virgilio (2020) performed a meta-analysis to compare IMRT with trans-oral robotic surgery (TORS) for the treatment of oropharyngeal squamous cell carcinoma.[31] Of the 5,624 total patients (IMRT, n=4,322; TORS, n=1,302), 3,433 were treated with concurrent chemotherapy and 826 received adjuvant treatment. The cumulative survival rates were 83.6% (99% CI 76.9 to 89.3%) and 91.3% (99% CI 81.2 to 97.8%) in the IMRT and TORS groups, respectively. The difference in disease-free survival between groups was statistically significant, favoring TORS (IMRT 79.6%, 99% CI 70.6 to 87.3%; TORS 89.4%, 99% CI 82.7 to 94.5%). The groups were not significantly different for feeding tube dependence or tracheostomy dependence rates.

Luo (2019) performed a systematic review and meta-analysis comparing conformal radiotherapy and IMRT for nasopharyngeal carcinoma.[32] From a search through November 2018, 13 eligible studies were identified. One was an RCT, one a prospective study, and the rest were retrospective. Compared patients treated with conformal radiotherapy, IMRT-treated patients had increased survival (OR=0.51, 95% CI=0.41 to 0.65, p<0.00001), increased locoregional control rate (OR=0.59, 95% CI=0.52 to 0.67, p<0.00001), and increased metastasis-free survival (OR=0.71, 95% CI=0.54 to 0.94, p=0.01).

Ursino (2017) published a systematic review of 22 studies (total n=1311 patients) evaluating swallowing outcomes in patients treated with 3D-CRT or IMRT for head and neck cancer.[33] The heterogeneity of the population limited analysis, but reviewers concluded that IMRT produced markedly better results than 3D-CRT in terms of swallowing impairments, aspiration, pharyngeal residue, and functional parameters, especially when swallowing-related organs at risk were specifically taken into account during IMRT treatment planning. The analysis was limited by a lack of standardized evaluation questionnaires, objective instrumental parameter scores, amount and consistency of bolus administration, and timing of evaluations.

In 2014, Marta reported on a systematic review and meta-analysis of five prospective Phase III randomized trials comparing IMRT to 2D-RT or 3D-CRT for head and neck cancer.[34] A total of 871 patients were randomized in these five studies to IMRT (n=434) versus 2D-RT or 3D-CRT (n=437). Xerostomia grade 2 to 4 was found to be significantly lower in IMRT than 2D-RT and 3D-CRT for all studies (hazard ratio = 0.76; 95% confidence interval: 0.66, 0.87; p<0.001). Locoregional control and overall survival was similar between IMRT and 2D-RT or 3D-CRT.

A comparative effectiveness review was published in 2010 on radiotherapy treatment for head and neck cancers by Samson from the BlueCross BlueShield Association (BCBSA) Technology Evaluation Center under contract with the Agency for Healthcare Research and Quality (AHRQ).[35] This report noted that based on moderate evidence, IMRT reduces late

xerostomia and improves quality of life domains related to xerostomia compared with 3D-CRT. The report also noted that no conclusions on tumor control or survival could be drawn from the evidence comparing IMRT with 3D-CRT. An update of the BCBSA report published in 2014 was consistent with and strengthened the findings of the original review on late xerostomia.[36]

Other systematic reviews have concluded similar findings as the previous systematic reviews for treatment of head and neck cancers.[37-40]

Randomized Controlled Trials

Tao (2020) performed an RCT comparing dose-escalated IMRT with 3D-RT in the context of concurrent chemoradiotherapy for the treatment of locally advanced head and neck squamous cell carcinoma.[41] Patients were randomized to receive 70 Gy in 35 fractions over seven weeks with 3D-RT or 75 Gy in 35 fractions with IMRT. Both groups also received three cycles of cisplatin at 100 mg/m2 during RT. A total of 188 patients were included. Most (85%) had oropharyngeal tumors and 73% were stage IVa. Median follow-up was 60.5 months. The decrease in xerostomia was statistically significant ($p<0.0001$), favoring IMRT. One-year rates of grade ≥2 xerostomia in the 3D-RT and IMRT groups were 63% and 23%, respectively. The three-year rates of ≥2 xerostomia in the 3D-RT and IMRT groups were 45% and 11%, respectively. No significant difference was identified between groups for locoregional progression (adjusted HR 1.13; 95% CI 0.64 to 1.98; $p=0.68$) or survival (adjusted HR 1.19; 95% CI 0.78 to 1.81; $p=0.42$).

Tandon (2018) published a non-blinded RCT which compared two fractionation schedules of IMRT for locally advanced head and neck cancer (LAHNC). The control arm was treated with simultaneous integrated boost (SIB-IMRT) and the study arm was treated with simultaneous modulated accelerated radiotherapy (SMART). The endpoint measures were toxicity, progression-free survival (PFS), and overall survival. Sixty patients with LAHNC were randomized to either SIB-IMRT (control arm) or SMART (study arm).[42] The SIB-IMRT group received 70, 63, and 56 Gy in 35 fractions to clinical target volumes (CTVs) 1, 2, and 3, respectively. The SMART group received 60 and 50 Gy to CTV 1 and CTV 3, respectively. No statistically significant differences in acute or late toxicities were found between the groups except in fatigue, which was experienced by 66.7% of the control group and 40.0% of the study group ($p=0.038$). At two years post-treatment, PFS was 53.3% and 80.0% ($p=0.028$) for the SIB-IMRT and SMART groups, respectively. Two-year overall survival was also higher for the SMART group, with rates of 60.0% vs 86.7% ($p=0.020$) for SIB-IMRT and SMART, respectively. The small sample sizes within subgroups, which result in greater standard errors and less power, may have prevented any meaningful interpretation of subgroup analysis. Also, due to cost, human papillomavirus (HPV) status was not part of the pretreatment workup; the treatment response and prognosis for HPV-positive tumors is considerably different compared to HPV-negative tumors, but this factor could not be included in the analysis.

Of the five phase three RCTs included in the meta-analysis by Marta, only one trial (Gupta, 2012) compared IMRT to 3D-CRT.[43] In 2016, long-term results from this trial were published. This study included 60 patients with squamous cell carcinoma of the head and neck and was powered to detect a 35% difference in toxicity between the treatments (85% vs 50%). The proportion of patients with salivary gland toxicity was lower in the IMRT group (59%) compared to the 3D-CRT group (89%; $p=0.009$). The percentage of patients with substantial weight loss was significantly lower in the IMRT group at one and two years. There were no significant differences between the two groups for acute dysphagia, mucositis, dermatitis, or requirements

for tube feeding. Xerostomia decreased over follow-up in both groups, but significant differences in late salivary toxicity persisted through five years. At two years after treatment, grade 2 or worse xerostomia was 0% in the IMRT group compared with 27.7% following 3D-CRT (p=0.017). At five years, salivary toxicity was 0% in the IMRT group compared with 16.7% following 3D-CRT (p=0.041). Locoregional control and overall survival were not significantly different between the two groups.

An RCT by Pow (2006) on IMRT for nasopharyngeal carcinoma (NPC) was published in 2006.[44] However, as previously noted, this RCT compared IMRT with conventional 2D-RT. In 2011, Nutting (2011) reported on the PARSPORT randomized phase three trial, which also compared conventional RT with parotid-sparing IMRT in 94 patients with T1 to 4, N0 to 3, M0 pharyngeal squamous cell carcinoma.[45] One year after treatment, grade 2 or worse xerostomia was reported in 38% of patients in the IMRT group, which was significantly lower than the reported 74% in the conventional RT group. Xerostomia continued to be significantly less prevalent two years after treatment in the IMRT group (29% vs 83%, respectively). At 24 months, rates of locoregional control, nonxerostomia late toxicities, and overall survival did not differ significantly.

The largest RCT on IMRT compared to 2D-RT was by Peng (2012).[46] The trial included 616 patients with NPC. At a median follow-up of 42 months (range 1 to 83 months), patients in the IMRT group had significantly lower radiation-induced toxicities. The five-year overall survival rate was 79% in the IMRT group compared to 67.1% in the 2D-RT group.

Nonrandomized Comparative Studies

Al Feghali (2020) reported a retrospective review of patients with T2N0M0 glottic squamous cell carcinoma treated with radiation therapy.[47] Of the 113 total patients, 85 received 3D-CRT and 28 received IMRT. Median follow-up was 91 months. Five-year local control for the 3D-CRT group and the IMRT group was 83% and 81%, respectively (p=0.76) and ultimate five-year local control for the 3D-CRT group and the IMRT group was 100% and 91%, respectively (p=0.83). No clinical or treatment variables were associated with better locoregional control. The only factor associated with better disease-specific survival was younger age (p=0.0068). There were no significant differences in adverse events or functional outcomes between groups.

Jirkovska (2019) performed a retrospective review to compare 3D-CRT and IMRT with simultaneous integrated boost (IMRT-SIB) for the treatment of locally advanced head and neck cancer.[48] Authors reported that in the 253 IMRT-SIB patients and 262 3D-CRT patients, there were no statistically significant differences in locoregional control or OS based on treatment, but there were significantly reduced acute toxicity and xerostomia in patients treated with IMRT-SIB.

Also in 2018, Bišof assessed radiation modalities in 24 patients with carcinoma of the nasopharynx. Authors compared IMRT-SIB with parotid gland-sparing 3D-CRT (ConPas 3D-CRT).[49] The IMRT-SIB group received significantly lower mean dose, dose to 50% parotid glands volume, and maximal dose to the spinal cord compared to the ConPas 3D-CRT group. The IMRT-SIB group also received superior coverage of planning target volumes. However, there were no significant differences between groups with respect to three-year OS (77% versus 81% for IMRT-SIB and ConPas 3D-CRT groups, respectively) or disease-free survival (51.9 and 70.7% for the IMRT-SIB and ConPas 3D-CRT groups, respectively).

A 2016 cross-sectional study by Huang included patients who had survived more than five years after treatment for NPC.[50] Of 585 NPC survivors, data were collected on 242 patients who met study selection criteria (no history of tumor relapse or second primary cancers, cancer-free survival >5 years, completion of the self-reported questionnaire). Treatments were given from 1997 to 2007, with transition to the IMRT system in 2002. One hundred patients were treated with IMRT. Prior to the institution of IMRT, treatments included 2D-RT (n=39), 3D-CRT (n=24), and 2D-RT plus 3D-CRT boost (n=79). Patients had scheduled follow-ups at three- to four-month intervals until five-years posttreatment; then, at six-month intervals thereafter. Late toxicities (e.g., neuropathy, hearing loss, dysphagia, xerostomia, neck fibrosis) were routinely assessed at clinical visits. At the time of the study, the mean follow-up was 8.5 years after 2D-RT or 3D-CRT, and 6.4 years after IMRT. The IMRT group had statistically and clinically superior results for both clinician-assessed and patient-assessed (global quality of life, cognitive functioning, social functioning, fatigue, and 11 scales of the head and neck module) outcomes with moderate effect sizes after adjusting for covariates (Cohen's d range, 0.47 to 0.53). Late toxicities were less severe in the IMRT group, with adjusted odds ratios of 3.2, 4.8, 3.8, 4.1, and 5.3 for neuropathy, hearing loss, dysphagia, xerostomia, and neck fibrosis, respectively. No significant differences in late toxicities were observed between the 2D-RT and the 3D-CRT groups.

In 2009, Vergeer published a report that compared IMRT and 3D-CRT for patient-rated acute and late xerostomia, and health-related quality of life (HRQOL) among patients with head and neck squamous cell carcinoma (HNSCC).[51] The study included 241 patients with HNSCC (cancers arising from the oral cavity, oropharynx, hypopharynx, nasopharynx, or larynx and those with neck node metastases from squamous cell cancer of unknown primary) treated with bilateral irradiation with or without chemotherapy. All patients were included in a program that prospectively assessed acute and late morbidity and HRQOL at regular intervals. Before October 2004, all patients were treated with 3D-CRT (n=150); starting in October 2004, 91 patients received IMRT. The use of IMRT resulted in a significant reduction of the mean dose to the parotid glands (27 gray [Gy] vs 43 Gy; $p<0.001$). During radiation, grade 3 or higher xerostomia at six weeks was significantly less with IMRT (20%) than with 3D-CRT (45%). At six months, the prevalence of grade 2 or higher xerostomia was significantly lower after IMRT (32%) versus 3D-CRT (56%). Treatment with IMRT also had a positive effect on several general and head and neck cancer-specific HRQOL dimensions.

Braam (2006) reported on a phase II study that compared IMRT to conventional RT in oropharyngeal cancer.[52] This study appeared to use 2D radiation therapy. The mean dose to the parotid glands was 48 Gy for RT and 34 Gy for IMRT. Both stimulated parotid flow rate and parotid complication (more than 25% decrease in flow rate) were greater in the RT group. At six months after treatment, 56% of IMRT patients and 81% of RT patients were found to have parotid complications.

Rusthoven (2008) compared outcomes with use of IMRT and 3D-CRT in patients with oropharyngeal cancer.[53] In this study, in which 32 patients were treated with IMRT and 23 with 3D-CRT, late xerostomia occurred in 15% of the IMRT patients and 94% of the 3D-CRT patients. There was also a trend toward improved locoregional control of the tumor with IMRT.

Hodge (2007) compared outcomes for patients with oropharyngeal cancer in the pre-IMRT era to those obtained in the IMRT era.[54] In this study of 52 patients treated by IMRT, the late xerostomia rate was 56% in the IMRT patients, compared to 63% in those that did not receive IMRT. The authors noted that outcomes in these patients improved at their institution since the

introduction of IMRT but that multiple factors may have contributed to this change. They also noted that even in the IMRT-era, the parotid-sparing benefit of IMRT cannot always be used; for example, in patients with bulky primary tumors and/or bilateral upper cervical disease.

Rades (2007) reported on 148 patients with oropharyngeal cancer treated with radiation therapy.[55] In this study, late xerostomia was noted in 17% of those treated with IMRT compared with 73% of those who received 3D-CRT and 63% of those who received standard radiation therapy.

Additional publications of IMRT for head and neck cancers consist of a number of small case series and non-randomized comparisons that generally report favorable outcomes of this treatment.[56-77]

Section Summary

In general, the evidence evaluating intensity-modulated radiotherapy (IMRT) for the treatment of head and neck cancer suggests that tumor control rates with IMRT are at minimum similar to those achieved with other non-IMRT techniques. In addition, although results are not uniform across all studies, most of the recent studies show a significant improvement in the rate of late xerostomia, a clinically significant complication of therapy that may result in decreased quality of life. Thus, published evidence shows an improvement in net health outcomes compared with non-IMRT methods.

THYROID CANCER

There are a small number of studies on use of IMRT for the treatment of thyroid cancer. In thyroid cancer, RT is generally used for two indications. The first indication is treatment of anaplastic thyroid cancer, and the second indication is potential use for locoregional control in patients with incompletely resected high-risk or recurrent differentiated (papillary, follicular, or mixed papillary-follicular) thyroid cancer. Anaplastic thyroid cancer occurs in a minority (<5%) of thyroid cancer.

The largest series comparing IMRT with 3D-CRT was published by Bhatia (2009)[78] This study reviewed institutional outcomes for anaplastic thyroid cancer treated with 3D-CRT or IMRT for 53 consecutive patients. Thirty-one (58%) patients were irradiated with curative intent. Median radiation dose was 55 Gy (range, 4 to 70 Gy). Thirteen (25%) patients received IMRT to a median 60 Gy (range, 39.9 to 69.0 Gy). The Kaplan-Meier estimate of overall survival at one year for definitively irradiated patients was 29%. Patients without distant metastases receiving 50 Gy or higher had superior survival outcomes; in this series, use of IMRT versus 3D-CRT did not influence toxicity.

Schwartz (2009) reviewed institutional outcomes for patients treated for differentiated thyroid cancer with postoperative conformal EBRT.[79] This was a single-institution retrospective review of 131 consecutive patients with differentiated thyroid cancer who underwent RT between January 1996 and December 2005. Histologic diagnoses included 104 papillary, 21 follicular, and six mixed papillary-follicular types. Thirty-four patients (26%) had high-risk histologic types and 76 (58%) had recurrent disease.

Extraglandular disease spread was seen in 126 patients (96%), microscopically positive surgical margins were seen in 62 patients (47%), and gross residual disease was seen in 15 patients (11%). Median RT dose was 60 Gy (range, 38 to 72 Gy). Fifty-seven patients (44%) were treated with IMRT to a median dose of 60 Gy (range, 56 to 66 Gy). Median follow-up was

38 months (range, 0 to 134 months). Kaplan-Meier estimates of locoregional relapse-free survival, disease-specific survival, and overall survival at four years were 79%, 76%, and 73%, respectively. On multivariate analysis, high-risk histologic features, M1 (metastatic) disease, and gross residual disease were predictors for inferior disease-specific and overall survival. IMRT did not impact survival outcomes but was associated with less frequent severe late morbidity (12% vs 2%, respectively), primarily esophageal stricture.

In 2011, Foote published a small case series (n=10) that reported the outcomes of the 10 anaplastic thyroid carcinoma (ACT) patients treated with an aggressive treatment combining IMRT, radiosensitizing, and adjuvant chemotherapy. The study found improved outcomes, including survival in stages IVA and IVB regionally confined ATC. Benefit in patients with stage IVC (metastatic) disease as well as the optimal chemotherapy regimen to use in conjunction with IMRT remains uncertain.[80]

Section Summary

Limited evidence exists on use of IMRT for thyroid cancer. The published literature consists of small case series with limitations. However, there is consensus that the use of IMRT for thyroid tumors may be appropriate in some circumstances such as for anaplastic thyroid carcinoma or for thyroid tumors that are located near critical structures (e.g., salivary glands, spinal cord). There is indirect evidence for the potential of IMRT to reduce harms. Therefore, IMRT may be considered for the treatment of thyroid cancers located in close proximity to organs at risk (esophagus, salivary glands, spinal cord) and three-dimensional conformal radiotherapy planning is not able to meet dose volume constraints for normal tissue tolerance.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

Central Nervous System

The National Comprehensive Cancer Network (NCCN) guidelines for the CNS (v.1.2023) section on meningiomas state that “Highly conformal fractionated RT techniques (eg 3D-CRT, IMRT, VMAT, proton therapy) are recommended to spare critical structures and uninvolved tissue.”[81] Regarding high-grade gliomas, the guidelines state that "conformal RT techniques, which include 3D-CRT and IMRT are recommended for performing focal brain irradiation. IMRT often will provide superior dosimetric target coverage and better sparing of critical structures than 3D-CRT." The guidelines also support the use of IMRT for reirradiation of gliomas, grade II infiltrative supratentorial astrocytoma/oligodendroglioma, leptomeningeal metastases, adult intracranial and spinal ependymoma, and adult medulloblastoma to reduce toxicity, achieve restricted margins/critical structure sparing, and provide superior dosimetric target coverage.

The NCCN guidelines for pediatric central nervous system cancers (v.2.2023) state in the Principles of Radiation Therapy Management, “In most instances intensity-modulated RT (IMRT) allows reduction of risk or magnitude of side effects from treatment.[82]

Head and Neck

The NCCN guidelines (v1.2024) on head and neck (H&N) cancers state, “Over the last 15 years, IMRT has displaced older techniques in the treatment of most H&N malignancies.”[83] The Principles of Radiation Therapy for treatment of the nasopharynx recommend IMRT. The

Principles of Radiation Therapy for other H&N cancer types and sites state IMRT is preferred; including for cancer of the oral cavity (including mucosal lip), the oropharynx, hypopharynx, glottic and supraglottic larynx, ethmoid sinus, maxillary sinus, very advanced head and neck cancer, occult primary, salivary gland tumors, and mucosal melanoma.

Thyroid

For thyroid cancer, the NCCN guidelines (v4.2023) state in the Principles of Radiation and Radioactive Iodine Therapy, External Beam Radiation Therapy that, “Conformal radiotherapy techniques including (IMRT) with simultaneous integrated boost (SIB) and image guidance are strongly encouraged in the adjuvant/definitive setting given the potential for reduced toxicity.”[84]

AMERICAN SOCIETY FOR RADIATION ONCOLOGY

The American Society for Radiation Oncology published 2022 guidelines on radiation therapy for IDH-mutant Grade 2 and Grade 3 diffuse glioma.[85] These guidelines include the following recommendations regarding IMRT:

- For patients with IDH-mutant WHO grade 2 and grade 3 diffuse glioma, IMRT/VMAT is recommended to reduce acute and late toxicity, especially for tumors located near critical OARs. (strong recommendation, low quality of evidence)
- For patients with IDH-mutant WHO grade 2 and grade 3 diffuse glioma, 3-D CRT is recommended as a treatment option, when IMRT/VMAT is unavailable. (strong recommendation, moderate quality of evidence)

AMERICAN COLLEGE OF RADIOLOGY AND AMERICAN SOCIETY FOR THERAPEUTIC RADIATION AND ONCOLOGY

The American College of Radiology (ACR) and the American Society for Therapeutic Radiation and Oncology (ASTRO) note that IMRT is a widely used treatment option for many indications including head and neck tumors. This guideline was last amended in 2014.[86]

MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE IN CANCER/INTERNATIONAL SOCIETY OF ORAL ONCOLOGY AND AMERICAN SOCIETY OF CLINICAL ONCOLOGY

The Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) and American Society of Clinical Oncology (ASCO) published a 2021 guideline on the prevention and management of salivary gland hypofunction and xerostomia induced by nonsurgical cancer therapies.[87] Regarding the use of IMRT, the guideline makes the recommendation that “Intensity-modulated radiation therapy should be used to spare major and minor salivary glands from a higher dose of radiation to reduce the risk of salivary gland hypofunction and xerostomia in patients with head and neck cancer (type: evidence-based; evidence quality: high; strength of recommendation: strong).”

CHINESE SOCIETY OF CLINICAL ONCOLOGY AND AMERICAN SOCIETY OF CLINICAL ONCOLOGY

The Chinese Society of Clinical Oncology (CSCO) and ASCO published a guideline on definitive-intent treatment of stage II-IVA nasopharyngeal carcinoma.[88] For patients with stage II-IVA nasopharyngeal carcinoma, the guideline recommends that IMRT with daily image guidance should be offered and that patients should be transferred to institutions with IMRT

available if necessary (Type: Evidence based, Benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong).

AMERICAN ASSOCIATION OF NEUROLOGICAL SURGEONS/CONGRESS OF NEUROLOGICAL SURGEONS JOINT SECTION ON TUMORS

In 2020, the American Association of Neurological Surgeons and Congress of Neurological Surgeons Joint Section on Tumors sponsored a systematic review and evidence-based clinical practice guideline update on the role of radiation therapy in the treatment of adults with newly diagnosed glioblastoma multiforme.[89] Among the 14 clinical questions that were examined, one question was specific for the use of IMRT: "In adult patients with newly diagnosed supratentorial glioblastoma is image-modulated RT or similar techniques as effective as standard regional RT in providing tumor control and improved survival?" The authors reviewing the clinical data concluded that: "There is no evidence that IMRT is a better RT delivering modality when compared to conventional RT in improving survival in adult patients with newly diagnosed glioblastoma. Hence, IMRT should not be preferred over the conventional RT delivery modality."

AMERICAN THYROID ASSOCIATION

The American Thyroid Association published guidelines for the management of patients with anaplastic thyroid cancer in 2021.[90] These guidelines contained the following recommendations regarding use of IMRT:

- Following R0 or R1 resection, we recommend that good performance status patients with no evidence of metastatic disease who wish an aggressive approach should be offered standard fractionation IMRT with concurrent systemic therapy.
  Strength of recommendation: strong; Quality of evidence: low.
- We recommend that patients who have undergone R2 resection or have unresectable but nonmetastatic disease with good performance status and who wish an aggressive approach be offered standard fractionation IMRT with systemic therapy.
  Strength of recommendation: strong; Quality of evidence: low.
- Among patients who are to receive radiotherapy for unresectable thyroid cancer or in the postoperative setting, IMRT is recommended.
  Strength of recommendation: strong; Quality of evidence: low.

SUMMARY

There is enough research to show that for the treatment of the central nervous system, head, neck, and thyroid of an area previously treated with radiation, intensity-modulated radiotherapy (IMRT) may provide improved outcomes for patients and lead to less adverse events compared to other radiotherapy techniques. Therefore, IMRT may be considered medically necessary for the reirradiation of central nervous system, head, neck, and thyroid tumors when policy criteria are met.

There is enough research to show that for the treatment of the central nervous system in pediatric patients, intensity-modulated radiotherapy (IMRT) may provide improved outcomes and lead to less adverse events compared to other radiotherapy techniques. Therefore,

IMRT may be considered medically necessary for the treatment of central nervous system tumors when policy criteria are met.

There is enough research to show that for individuals with brain tumor metastases, hippocampal-avoiding intensity-modulated radiotherapy (IMRT) may provide improved outcomes for some patients and lead to less adverse events compared to other radiotherapy techniques. Therefore, IMRT may be considered medically necessary for the treatment of brain tumor metastases when policy criteria are met.

There is enough research to show that intensity-modulated radiotherapy (IMRT) provides tumor control rates comparable to existing radiotherapy techniques for head and neck cancers and lymphomas in the head and neck region, excluding follicular and malt and marginal zone lymphomas. In addition, research shows improvements in complication rates. Therefore, IMRT may be considered medically necessary for the treatment of head and neck cancers and lymphomas in the head and neck region when policy criteria are met.

The current research on the use of intensity-modulated radiotherapy (IMRT) for the treatment of thyroid cancer is limited. However, IMRT may reduce the risk of exposure of radiation to critical nearby structures, such as the spinal cord, salivary glands, and esophagus. Therefore, IMRT may be considered medically necessary for the treatment of thyroid cancer when policy criteria are met.

For all other indications, intensity-modulated radiotherapy (IMRT) has not been shown to improve net health outcomes compared to other treatment modalities. Therefore, except in the select group of patients identified in the policy criteria, IMRT is not medically necessary for the treatment of all other central nervous system, head, neck, and thyroid cancers.

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CODES

NOTE: The correct code to use for image fusion performed to provide enhanced delineation of target and normal critical structures is CPT code 77399 (Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services); however, it is considered part of the treatment planning.

Codes	Number	Description
CPT	77301	Intensity modulated radiotherapy plan, including dose volume histograms for target and critical structure partial tolerance specification
	77338	Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan
	77385	Intensity modulated radiation treatment deliver (IMRT), includes guidance and tracking, when performed; simple
	77386	;complex
HCPCS	G6015	Intensity modulated treatment delivery, single or multiple fields/arcs, via narrow spatially and temporally modulated beams, binary, dynamic mlc, per treatment session
	G6016	Compensator-based beam modulation treatment delivery of inverse planned treatment using 3 or more high resolution (milled or cast) compensator, convergent beam modulated fields, per treatment session

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