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Highlights from the 2025 ASCO annual meeting: central nervous system

Raquel Fontes

Unidade Local de Saúde de Braga, Braga, Portugal

Stereotactic radiation versus hippocampal avoidance whole brain radiation in patients with 5-20 brain metastases: A multicenter, phase 3 randomized trial

Prior trials have demonstrated that stereotactic radiosurgery (SRS)/stereotactic radiotherapy (SRT) yields better outcomes than traditional whole brain radiotherapy (WBRT) in patients with 1-4 brain metastases, and that hippocampal avoidance WBRT (HA-WBRT) is superior to traditional WBRT. Despite that, trials for more than 4 brain metastases are lacking, and there are no head-to-head comparisons between stereotactic radiation and HA-WBRT.

In a clinical science symposium, Dr Ayal Aizer presented the results of a multicenter, phase 3 trial that compared stereotactic radiation versus HA-WBRT in patients with 5-20 brain metastases. The primary endpoint was symptom severity and interference in daily activities, which was accessed by an *MD Anderson symptom inventory brain tumor questionnaire*, at baseline and after 6 months. Other outcomes were performance status, ability to complete activities of daily living, neurocognitive function, recurrence, and salvage therapy, among others. Between april 2017 and may 2024, 196 patients were enrolled, with a median number of brain metastases of 14, mainly from non-small cell lung cancer (47%) or breast cancer (20%). This study demonstrated that SRS/SRT reduces symptom severity and interference with daily function compared to HA-WBRT, without compromising survival. Patients experienced less symptoms such as pain, nausea, sleep, memory, speech, and humor disorders. Similarly, the ability to work and self-care was less impaired. Performance status, ability to complete daily activities, and many neurocognitive domains were also spared by SRS/SRT as opposed to HA-WBRT. Thus, the authors propose that SRS/SRT should represent the radiotherapeutic standard of care for most patients with 5-20 brain metastases.

Initial report of memory avoidance WBRT (MA-WBRT) to treat brain metastases: A prospective phase 2 trial

Still within the scope of brain radiotherapy (RT), a prospective phase 2 trial was presented as a poster and compared HA-WBRT plus memantine with "memory avoidance" WBRT. This approach is based on the knowledge that there are other structures, beyond the hippocampus, with important roles in memory and cognition, including the corpus callosum, fornix, amygdala, hypothalamus, and pituitary. They have a low propensity for harboring brain metastases and can be safely spared in an RT plan without increasing the risk of relapse and, hopefully, with less cognitive decline. Patients with more than 15 brain metastases were randomized to either MA-WBRT (30 Gy in 10 fractions) plus memantine (with or without neuropsychological evaluation and intervention). Cognition was measured by multiple tests evaluating verbal learning and memory, verbal fluency, and executive function. Results were compared with a historical control of the phase 3 NRG

Correspondence:
Raquel Fontes
E-mail: ana.r.fontes@ulsb.min-saude.pt

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CCOO1 trial, conducted in 2020, which validated the standard of treatment with HA-WBRT plus memantine for patients with brain metastases. The cognitive decline rates of 17.2% and 48.3% at 3 and 6 months for patients receiving MA-WBRT compared very favorably to 3 and 6-month cognitive decline rates of 50% and 60% that were seen on NRG CC001 with HA-WBRT. In addition, MA-WBRT does not appear to significantly increase the risk of intracranial failure. These promising preliminary results must be fully evaluated in a randomized phase 3 trial.

Final clinical and molecular analysis of the EORTC randomized phase 3 intergroup CATNON trial on concurrent and adjuvant temozolomide (TMZ) in anaplastic glioma without 1p/19q codeletion: NCT00626990

This year, the final clinical and molecular analysis of the CATNON trial, which studied the role of concurrent and adjuvant TMZ in anaplastic glioma without 1p/19q codeletion, was presented at ASCO. This trial, with a unique 2^2 factorial design, randomized 751 adult patients with newly diagnosed non-codeleted anaplastic glioma to either: 59.4 Gy RT alone; RT with concurrent TMZ; RT and 12 cycles of adjuvant TMZ, or RT with both concurrent and 12 cycles of adjuvant TMZ. In 660 patients, IDH status could be determined: isocitrate dehydrogenase (IDH) was mutant (mt) in 444 tumors and wild type (wt) in 216 tumors.

After a median follow-up of 10.9 years, the benefit from adjuvant TMZ on overall survival (OS) in patients with IDH-mut tumors was clear. Still, no benefit of concurrent TMZ was observed regardless of IDH mutation status. The benefit of adjuvant TMZ was limited to patients with anaplastic glioma IDH-mut, of which 45% were still alive, with a median OS of 12.5 years. In exploratory analysis, molecular factors of known prognostic significance, such as high-copy number amplification of PDGFR and CDK4, homozygous deletion of the CDKN2A/B locus, or total copy number alterations, were not predictive of benefit from TMZ. In summary, the standard of post-operative care in patients with high-grade IDHmt astrocytoma should be RT followed by 12 cycles of adjuvant TMZ.

Risk of intracranial hemorrhage with direct oral anticoagulants (DOACs) versus low molecular weight heparin (LMWH) in patients with cancer-associated thrombosis and brain metastases

Finally, some notes on a very important work for clinical practice.

Cancer-associated thrombosis is a major complication in cancer patients, significantly increasing morbidity and mortality. There is also an increased risk of bleeding in patients with cancer on anticoagulants compared with those without cancer, and patients with brain metastases, particularly those with high-risk primary tumors, have an increased risk of intracranial hemorrhage. However, only a minority of patients with brain metastases are included across landmark trials.

This retrospective study enrolled over 8400 patients with solid tumors, mainly with lung (51.9%) and breast (16.2%) cancer, who developed a thromboembolic event within 6 months of brain metastases diagnosis. Therapeutic approaches were compared between DOACs, such as apixaban, rivaroxaban, edoxaban, and LMWH, regarding intracranial hemorrhage incidence, bleeding events, intensive care unit (ICU) admissions, and all-cause mortality. DOACs were associated with a statistically significant lower risk of intracranial hemorrhage incidence (hazard ratio: 0.855, 95% confidence interval: 0.731-0.999, $p = 0.049$), supporting their role as a viable and well-tolerated alternative. In addition, significantly lower rates of ICU admission (16.7% vs. 20.3%; $p = 0.001$) and all-cause mortality at 12 months (42.4% vs. 48.9%; $p = 0.001$) were observed in the DOAC group, indicating that they also have a favorable profile and can be safely used, without significant differences by cancer type.

In general, all these studies highlight the path that is being traced in oncology, toward more individualized and patient-centered strategies.