EMBRACE II: Tumor Regression and Target Volume Adaptation in Locally Advanced Cervical Cancer

Insights from Dr. Johannes Knoth

The EMBRACE II trial was a prospective, multicenter study designed to evaluate and refine radiotherapy approaches for locally advanced cervical cancer (LACC). Building on EMBRACE I, the study focused on incorporating advanced imaging, adaptive planning, and modern delivery techniques to improve treatment precision and reduce toxicity. More than 1,300 patients were enrolled across multiple international centers. The trial investigated the use of MRI and PET-CT for staging, adaptive target volume definition, and conformal radiotherapy techniques such as Image-Guided Radiation Therapy–Intensity-Modulated Radiation Therapy (IGRT-IMRT), Lymph Node–Simultaneous Integrated Boost (LN-SIB), Para-Aortic Radiation Therapy (PAO-RT), and Magnetic Resonance–Image-Guided Adaptive Brachytherapy (MR-IGABT). The study generated detailed data on clinical outcomes, treatment-related toxicity, and tumor response dynamics in LACC. Its findings have contributed to shaping current standards of care and emphasize the value of personalized, image-guided treatment strategies.

In this interview, Dr. Johannes Knoth, radiation oncologist at the Medical University of Vienna, member of the EMBRACE group, and one of the study's authors, shares insights from his presentation "Target Volume and Tumour Regression Dynamics in Locally Advanced Cervical Cancer: Report from the Prospective EMBRACE II Study" delivered at the ESTRO Congress 2025.

Johannes Knoth

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Dr. Knoth, thank you for taking the time to speak with us. For readers less familiar with it, how would you briefly describe the goals and design of the EMBRACE II trial, and how it builds on the original EMBRACE study?

EMBRACE II is a large, prospective, international multicenter cohort study that enrolled more than 1,300 patients with locally advanced cervical cancer across 49 institutions worldwide. It was designed to formalize a modern image-guided workflow that integrates IGRT-IMRT with risk-adapted nodal boosts and para-aortic options, concurrent cisplatin chemotherapy, and MRI-guided adaptive brachytherapy (BT). The protocol specifies a well-defined hierarchy of target volumes, beginning with the gross tumor volume and extending to tight 5 mm margins supported by daily image guidance. Compared with EMBRACE I, the second trial codified the

systematic use of MRI and PET-CT, adaptive planning, and multiparametric dose constraints for External Beam Radiation Therapy (EBRT) and brachytherapy, with the overarching aim of improving treatment precision, reducing morbidity, and setting new international benchmarks for outcomes in this disease.

"With its reproducible and reliable protocol, EMBRACE II has already set a new standard of care"

Your recent ESTRO 2025 presentation focused on tumor regression and target volume dynamics. What were the key messages you hoped to share with the radiation oncology community?

The presentation emphasized that EMBRACE II has for the first time provided robust, multicenter reference values for EBRT volumes and nodal boosts, along with detailed data on primary tumor regression. The median elective PTV45 Gy for the large pelvis was approximately 1,400 cm^3, while patients with para-aortic involvement reached a median of around 1,750 cm^3. Nodal target volumes were also quantified, with a median of 3.3 cm^3 for gross nodal disease and about 14 cm^3 per boosted node. Perhaps most strikingly, the study documented the dramatic regression of primary tumors during treatment, with the gross tumor volume shrinking from a median of 37 cm^3 at baseline to only 5 cm^3 at the time of brachytherapy, corresponding to nearly a 90% reduction overall. The high-risk CTV decreased from around 59 to 27 cm^3 in the same interval. These regression dynamics were strongly stage-dependent, being less pronounced in more advanced tumors, and have direct consequences for brachytherapy planning.

Together, these quantitative benchmarks serve to harmonize practice, reduce inter-institutional variability, and provide clinicians with reference values for both planning and quality assurance.

Based on your analysis, how do tumor shrinkage patterns during treatment affect target volume definition and adaptive planning strategies?

The shrinkage patterns observed in EMBRACE II underline the importance of an adaptive strategy that anticipates change. In the majority of patients, the marked regression of tumor volume allows for a tighter, MRI-based delineation of the high-risk CTV at brachytherapy, thereby enabling highly conformal dose delivery while sparing adjacent organs. In contrast, patients with very advanced disease, particularly T3b and T4 stages, show more limited proportional regression. For these women, substantial residual disease often remains in the parametria or vagina, and brachytherapy planning must account for this with broader and frequently interstitial implants. In other words, the study demonstrates that adaptive radiotherapy in cervical cancer is not only possible but necessary: it improves conformity in smaller, regressing tumors while ensuring comprehensive coverage of persistent disease in more extensive stages.

In practice, how often should clinicians consider re-evaluating volumes during treatment, and what are the main criteria or triggers for adaptation?

Within EMBRACE II, two re-evaluation points proved universal: the initial EBRT planning, which integrates MRI and PET-CT for accurate

staging and target definition, and the re-imaging at the time of brachytherapy, when tumor regression is explicitly assessed and translated into adapted volumes and implant strategy. Additional imaging during EBRT may be justified in selected cases—for example, when bulky baseline disease or an advanced stage predicts limited shrinkage, when rapid anatomical changes such as uterine position or organ filling may threaten coverage, or when early assessment is needed to prepare a complex brachytherapy implant. While not mandatory in every patient, these mid-course checks can provide valuable information, particularly in high-risk cases, and reflect the adaptive ethos that EMBRACE II has established as a standard of care.

What advice would you give to departments that want to implement adaptive strategies from EMBRACE II but have limited access to MRI or advanced planning tools?

Even in resource-limited settings, much of the EMBRACE II concept can be implemented.

A first step is to adopt the explicit target hierarchy defined in the protocol, with gross tumor and nodal disease leading to risk-adapted elective fields and carefully margin-reduced planning target volumes justified by daily image guidance. A single high-quality MRI before treatment can provide a critical anatomical reference, even if MRI is not available for brachytherapy. In such cases, clinicians may rely on the combination of diagnostic MRI, careful clinical examination, and CT-based planning to approximate the regression-adapted high-risk CTV.

EMBRACE II also provides quantitative benchmarks for EBRT and nodal volumes, which can serve as internal quality assurance references, ensuring that volumes and doses remain within expected ranges.

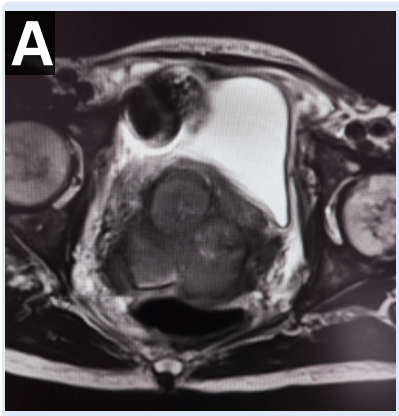
Finally, building collaborative referral pathways to centers with MRI-based brachytherapy expertise can help patients with complex disease benefit from advanced adaptive implants. Step by step, these measures allow departments to align with EMBRACE II principles even before achieving full MR-guided capability.

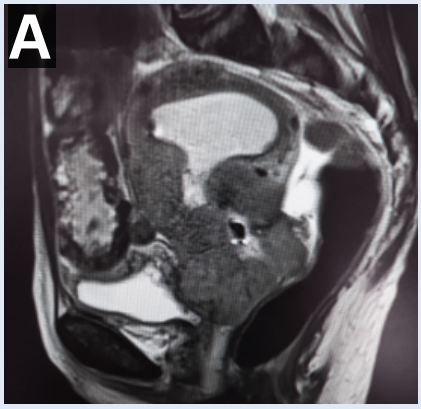
To conclude, what do you see as the next important research questions or developments in adaptive radiotherapy for cervical cancer, and how do you imagine the field evolving in the coming years?

Looking ahead, several developments appear particularly promising. One area is the prognostic role of regression metrics: EMBRACE II has shown that shrinkage differs significantly by stage, and building on this, JC Lindegaard and colleagues have proposed a continuous T-score, which integrates both initial tumor size and regression dynamics as a potential prognostic marker. This approach could allow clinicians to stratify patients not only by categorical stage but also by quantitative tumor biology and to adapt dose concepts accordingly.

Another important direction is the integration of automation and artificial intelligence, which can facilitate adaptive workflows, reduce inter-observer variability in contouring, and make EMBRACE II principles more accessible even in centers without routine MRI.

Finally, a more intelligent integration of EBRT and brachytherapy is on the horizon: by using early regression patterns and nodal burden, clinicians may individualize EBRT field designs,





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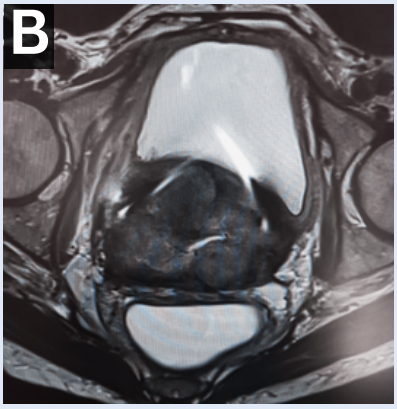
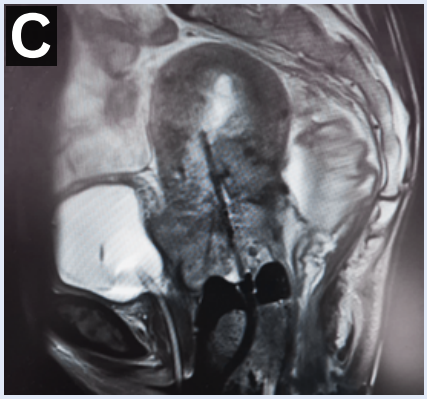
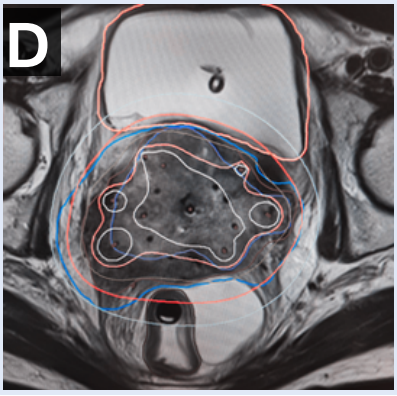
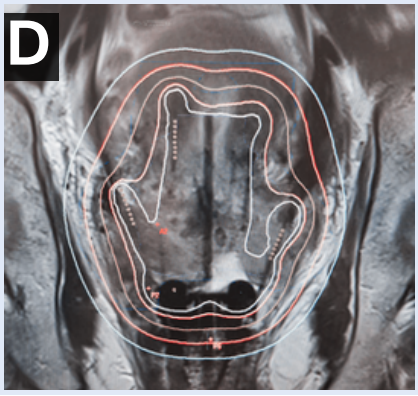
48 Years old patient with Cervical Cancer T4 N1 M0

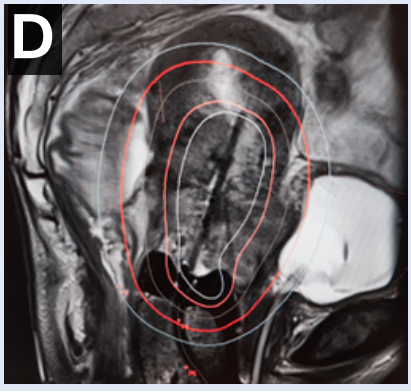


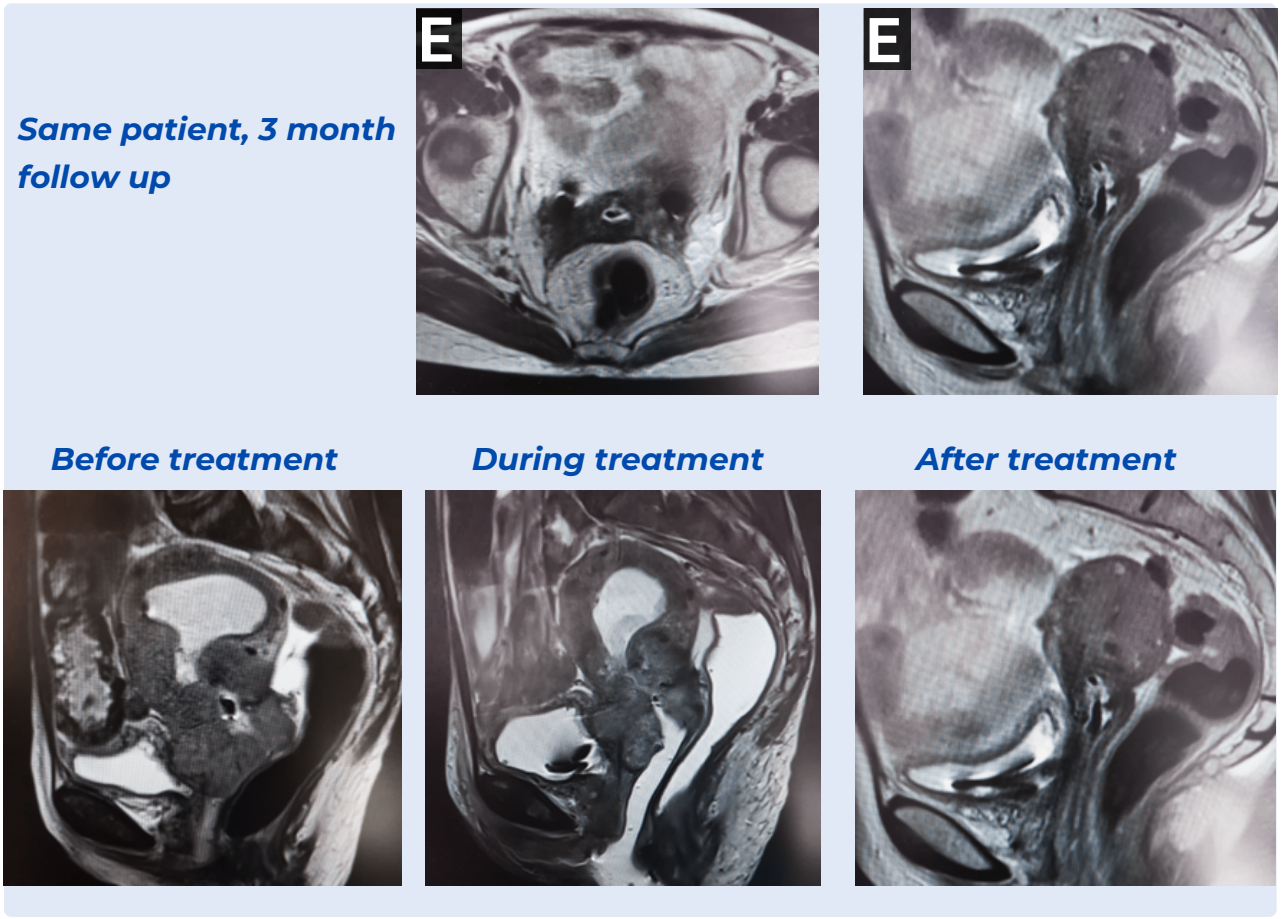
A - Before EBRT
B - After EBRT, Before BT
C - During BT
D - Dose Distribution for BT
E- 3 month Follow up











nodal boosts, and implant strategies earlier in the pathway. Taken together, these advances point to a future where adaptive, image-guided, and data-driven radiotherapy becomes the norm, building on EMBRACE II's demonstration of excellent survival, high local control, and very low morbidity. With its reproducible and reliable protocol, EMBRACE II has already set a new standard of care; the next steps will refine personalization even further.