# Phase-III INTERLACE Trial: A Study Requires Post-Hoc Analysis of Subgroups with Locally-Advanced Cervical Cancer

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Braz J Oncol 2025;21:s00451811731.

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To the Editor,

In recent years, few studies have provided oncological outcomes with the potential to change clinical practice for patients with cervical cancer, leaving the standard model of combined chemoradiotherapy for locally-advanced disease largely unchanged. Over the past year, 2 phase-III clinical trials—KEYNOTE-A18[1] and INTERLACE[2]—have introduced new evidence with the potential to reshape this consolidated standard. The addition of immunotherapy to standard treatment demonstrated a significant improvement in progression-free survival for patients with high-risk, locally-advanced cervical cancer,[1] while the inclusion of induction chemotherapy followed by chemoradiotherapy also showed promising results.[2]

In 2023, the INTERLACE study was presented at the European Society for Medical Oncology (ESMO) annual congress, with preliminary results generating enthusiasm within the scientific community. On October 14, 2024, the final version was published in *The Lancet*, titled "Induction chemotherapy followed by standard chemoradiotherapy versus standard chemoradiotherapy alone in patients with locally-advanced cervical cancer (GCIG INTERLACE): An international, multicentre, randomised phase 3 trial".[2,3]

The study included 500 eligible patients from 32 centers across developed countries (Italy and England) and developing countries (Brazil, India, and Mexico), aged $\geq$ 18 years, with a diagnosis of cervical cancer staged FIGO IB1 with lymph node metastasis, IB2 to IVa (excluding IIIA).[2] Considering the staging eligibility of the included patients, it is evident that distinct groups are represented in the study, potentially influencing subgroup analyses to identify those who benefit most from induction therapy versus overtreatment. Patients with evident, macroscopic lymph node involvement (cN+) are more likely to receive a boost dose via teletherapy, increasing toxicity, morbidity, and negatively affecting prognosis and quality of life. This raises a new hypothesis: could patients with cN+ disease benefit more from induction therapy?

The randomization followed a 1:1 ratio, with one arm receiving standard chemoradiotherapy (CRT) followed by brachytherapy, and the other arm undergoing induction chemotherapy (weekly paclitaxel 80 mg/m$^2$ and carboplatin AUC2 for 6 weeks), followed by CRT and brachytherapy initiated within 7 days. The standard model consisted of weekly cisplatin 40 mg/m$^2$ for 5 weeks combined with teletherapy at 40 to 50.4 Gy in the pelvic field, followed by complete gynecological brachytherapy (boost), preferably completed within 8 weeks. In the INTERLACE trial, external radiotherapy employed 3D conformational or intensity-modulated techniques (IMRT), while gynecological brachytherapy utilized 2D or 3D techniques, with dose prescription at point A (78 Gy). Over a short follow-up period (67 months), the study demonstrated increased overall survival ($p = 0.015$) and progression-free survival ($p = 0.013$) with the addition of induction chemotherapy, albeit with increased grade III to IV toxicity.[2]

The use of varying radiotherapy techniques creates a different landscape for dose distribution and preservation of at-risk structures, potentially impacting oncological outcomes. The addition of induction chemotherapy to patients receiving 3D conformational radiotherapy (3DCRT) followed by 2D brachytherapy may have contributed to improved survival due to less advanced dose-conformation technology. This observation is critical, as despite the study

**received**
July 11, 2025
**accepted**
July 21, 2025

**DOI** https://doi.org/10.1055/s-0045-1811731.
**ISSN** 2526-8732.



Thieme Revinter Publicações Ltda., Rua Rego Freitas, 175, loja 1, República, São Paulo, SP, CEP 01220-010, Brazil

presenting induction therapy as more accessible for healthcare services, only three developing countries were included, where treatment delivery may rely more heavily on less conformal techniques, particularly in public services. Additionally, it is important to note that initiating standard treatment within seven days postinduction could pose a challenge for high-volume centers with limited radiotherapy equipment.

The promising results from the INTERLACE trial have generated new hypotheses. A post-hoc analysis of this study could help address some of the key questions regarding chemoradiotherapy treatment for patients with locally-advanced cervical cancer.

### Clinical Trials
None.

### Funding
The authors declare that they did not receive funding from agencies in the public, private, or non-profit sectors to conduct the present study.

### Authors' Contributions
HSBO: conceptualization, data curation, formal analysis, project administration, validation, visualization, writing – original draft, writing – review & editing; SDB: formal analysis, project administration, validation, visualization, writing – original draft, writing – review & editing; MJA: project administration, validation, visualization, writing – original draft, writing – review & editing; ELP: validation, visualization, writing – original draft, writing – review & editing; TSY: validation, visualization, writing – original draft, writing – review & editing.

### Conflict of Interests
The authors have no conflict of interests to declare.

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