Cancer Biol Med 2026. doi: 10.20892/j.issn.2095-3941.2026.0139

PERSPECTIVE

Less is more: patients with cervical cancer benefit from de-escalated chemotherapy plus immuno-targeted therapies

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Introduction

Cervical cancer remains a global health burden, and, despite prevention and screening efforts, many patients still experience locally advanced disease or relapse after definitive therapy[1]. Contemporary management is multidisciplinary and adapted to cancer stage[2]. For locally advanced cervical cancer, guideline-recommended care focuses on definitive radiotherapy with concurrent platinum chemotherapy and brachytherapy, and systemic intensification strategies are increasingly being evaluated in carefully defined high-risk groups[3]. In the metastatic, persistent, or recurrent setting, systemic therapy has been reshaped over the past decade by the addition of targeted agents and immunotherapy to platinum-based doublets; however, heterogeneous treatment durability and substantial cumulative toxicity persist, particularly when multi-cycle cytotoxic therapy is used as the dominant therapeutic backbone.

The modern era of systemic therapy in cervical cancer has been defined by 2 advances. First, the addition of anti-angiogenic therapy to chemotherapy has improved survival and established VEGF targeting as an effective component of first-line treatment[4]. Second, immune checkpoint blockade was incorporated as a first-line therapy, on the basis of findings that pembrolizumab, combined with platinum-based chemotherapy with or without bevacizumab, increased progression-free survival (PFS) and overall survival (OS) in patients with PD-L1-positive disease, thereby confirming that immune modulation can translate into clinically meaningful benefit in cervical cancer[5]. Combining PD-L1 blockade with bevacizumab and chemotherapy further reinforced that immune-targeted triplets can produce strong survival signals[6]. In parallel, immunotherapy has become part of the management of earlier-stage disease, as exemplified by a randomized phase 3 trial showing benefit from adding pembrolizumab to chemoradiotherapy followed by maintenance pembrolizumab in patients with newly diagnosed high-risk locally advanced cervical cancer[7]. These advances prompt an important question in precision cervical cancer therapy: after immune-targeted therapy is active, must chemotherapy still remain at full intensity, or can it be rationally reduced while preserving efficacy and improving tolerability?

A recent study by Xu et al. in *Cancer Discovery* was aimed at addressing this paradox between efficacy and treatment burden by testing a de-escalated chemotherapy strategy integrated with an immune-targeted therapy, guided by an analysis of the immune contexture associated with response[8]. In this Perspective, we use our results as a starting point to propose a clinically testable path toward intensity-tailoring strategies in advanced cervical cancer, emphasizing 2 features that we believe carry the most immediate translational value: chemotherapy de-escalation as a treatment principle and the association between tertiary lymphoid structures (TLSs) and benefit from our regimen. A schematic overview of the de-escalated induction-to-maintenance strategy and the proposed TLS-guided precision framework is shown in **Figure 1**.

Immuno-targeted combinations are rapidly advancing, but chemotherapy intensity has not been sufficiently questioned

In first-line recurrent or metastatic cervical cancer, platinum-based doublets are frequently delivered for multiple cycles, often in combination with targeted therapy and now together with immunotherapy. The field has largely focused on escalation by addition rather than optimization

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Received February 12, 2026; accepted May 19, 2026;
published online June 22, 2026.
Available at www.cancerbiomed.org
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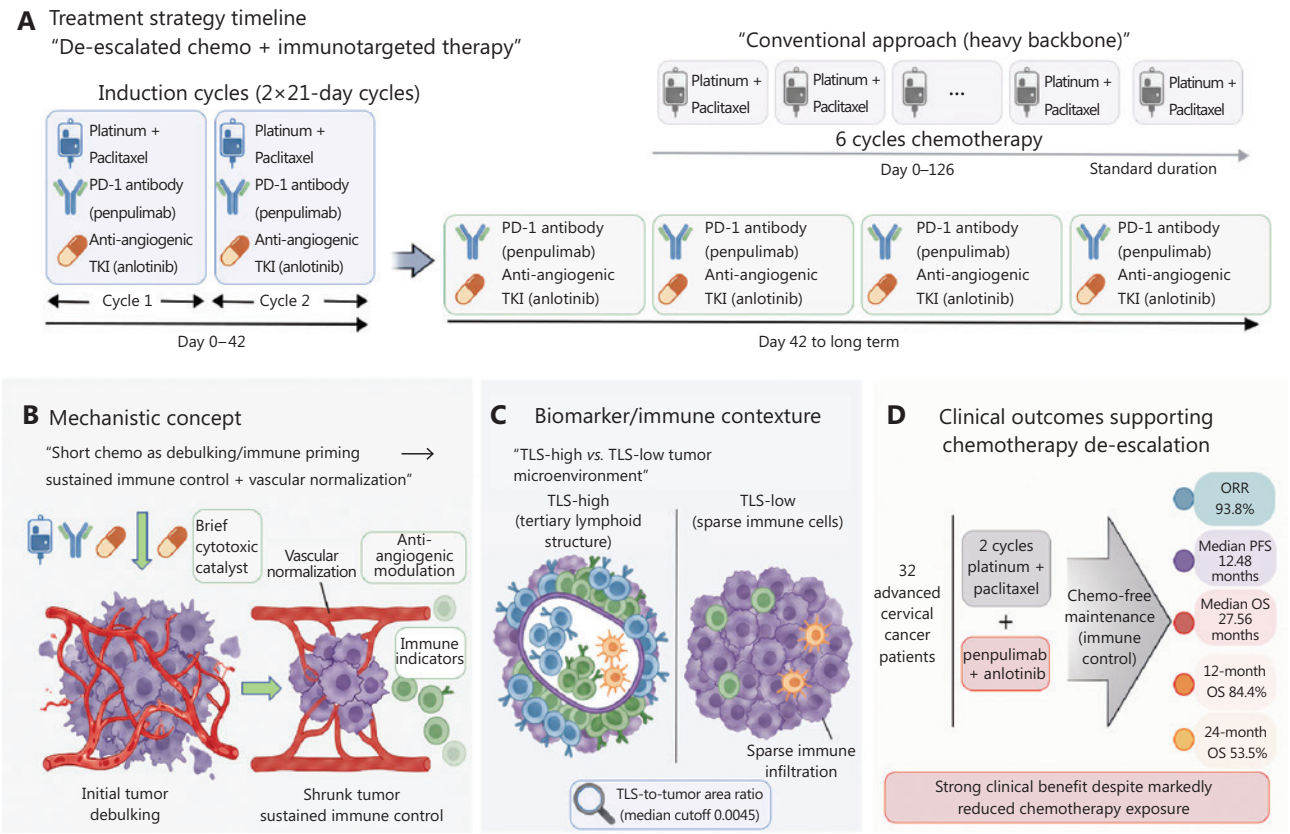


Figure 1 Conceptual framework for chemotherapy de-escalation enabled by early immuno-targeted therapy, and associated with TLSs, in advanced cervical cancer. (A) De-escalated induction-to-maintenance regimen. Schematic timeline of the first-line strategy featuring only two 21-day induction cycles of platinum plus paclitaxel combined with the PD-1 inhibitor penpulimab and the multi-target anti-angiogenic TKI anlotinib, followed by chemotherapy-free maintenance with penpulimab plus anlotinib for responders. This design intentionally contrasts with conventional multi-cycle chemotherapy (typically 4 to 6 cycles) as the dominant therapeutic backbone. (B) Mechanistic rationale for "less is more". The model reframes chemotherapy as a brief initiator to achieve early tumor debulking and immune priming and relies on sustained immuno-targeted therapy supported by anti-angiogenic modulation to achieve durable disease control. (C) TLS-guided precision medicine concept. Pretreatment tumors are stratified by immune organization according to the TLS-to-tumor area ratio; greater TLS abundance (median cutoff 0.0045) is associated with significantly better PFS and a trend toward improved OS, thus supporting TLSs as a candidate biomarker to identify patients likely to benefit from an immune-centered, de-escalated backbone. (D) Clinical outcomes supporting chemotherapy de-escalation. Summary of the robust efficacy observed in a cohort of 32 patients with advanced cervical cancer. Delivering only 2 cycles of induction chemotherapy followed by chemotherapy-free immune maintenance yielded an objective response rate (ORR) of 93.8%, a median PFS of 12.48 months, and a median OS of 27.56 months (with 12-month and 24-month OS rates of 84.4% and 53.5%, respectively). These metrics highlight strong and durable clinical benefit despite markedly decreased cytotoxic exposure.

by subtraction. Because the survival benefit of adding bevacizumab to chemotherapy in GOG-240 exceeds that of multi-cycle cytotoxic therapy, a pattern has been established in which chemotherapy remains the central scaffold[4]. The same paradigm was examined in the KEYNOTE-826 trial, in which pembrolizumab was layered onto chemotherapy with or without bevacizumab, and again without decreasing cytotoxic exposure[5]. The BEATcc trial similarly combined atezolizumab with bevacizumab and chemotherapy, thus underscoring that the dominant development strategy has been to intensify combinations while maintaining conventional chemotherapy intensity[6].

However, across these regimens, toxicity, quality of life, and treatment discontinuations remain clinically consequential, and real-world practice often reflects compromises in dose intensity, schedule, or duration. This issue is not simply one of tolerability but also of precision. If a subset of patients can experience deep and durable benefit from immune-targeted

therapy, prolonged cytotoxic exposure might represent overtreatment for some patients, whereas other patients might still require escalation or alternative strategies. The field therefore needs biomarkers and prospective clinical trials that can support the rationale for tailoring intensity, rather than assuming that maximal chemotherapy is always required.

The locally advanced setting highlights the same dilemma in a different form. Standard-of-care chemoradiotherapy is effective for many patients, yet recurrence risk remains high in selected populations, and intensification has been pursued. Current guidelines provide a structured framework for radiotherapy and concurrent chemotherapy, whereas ongoing and recently positive trials suggest that adding immunotherapy might improve outcomes for high-risk locally advanced disease[3,7]. Simultaneously, not all immunotherapy plus chemoradiotherapy strategies succeed, as demonstrated by the CALLA trial of durvalumab with chemoradiotherapy; therefore, regimen design and patient selection matter[9]. These stage-spanning experiences support a broader concept: if immune engagement is critical, we should optimize how cytotoxic therapy is used to enable immune mediated control rather than automatically maximizing chemotherapy exposure.

Reframing the backbone: a short induction chemotherapy phase followed by chemotherapy-free immune-targeted maintenance

The prospective evaluation of a first-line regimen built around a de-escalated induction phase and a chemotherapy-free maintenance phase demonstrated the feasibility of this intensity-tailoring approach in advanced cervical cancer. The induction consisted of only 2 cycles (21 days each) of platinum plus paclitaxel combined with the PD-1 inhibitor penpulimab and the multi-target anti-angiogenic tyrosine kinase inhibitor anlotinib, followed by maintenance penpulimab plus anlotinib[8]. This design departed from the conventional approach of delivering at least 6 cycles of chemotherapy as the principal driver of response and instead treated chemotherapy as a brief initiator of tumor debulking and immune priming, while relying on sustained immune-targeted therapy to achieve long-term disease control.

Clinical outcomes demonstrated a high objective response rate and encouraging time-to-event outcomes despite limiting chemotherapy to 2 cycles. Among 32 efficacy-evaluable patients, the objective response rate was 93.8%; at a median follow-up of 14.6 months, the median PFS was 12.48 months, and at a median follow-up of 20.0 months, the median OS was 27.56 months. The 12-and 24-month OS rates were 84.4% and 53.5%, respectively. Although cross-trial comparisons must be made cautiously, these signals were notably achieved with markedly decreased chemotherapy exposure, which is the central novelty and the principal message of our work. This framework hinges on the premise that the field should ask not only whether new agents can be added to the standard backbone but also whether the backbone itself can be safely de-escalated when effective immune-targeted therapy is incorporated from the start.

Safety remains an essential component of interpreting any de-escalation strategy. Treatment-related adverse events were consistent with the multi-agent nature of the regimen: grade 3 or higher treatment-related adverse events occurred in 76.5% of patients, and treatment discontinuation due to treatment-related adverse events occurred in 2.9% of patients. These findings highlight that de-escalation of chemotherapy does not automatically translate to low toxicity, particularly when immunotherapy and anti-angiogenic therapy are combined. Simultaneously, decreasing chemotherapy cycles can still be clinically meaningful, because cumulative toxicities, such as neuropathy, marrow reserve depletion, and prolonged recovery, may be driven by repeated cytotoxic exposure, and because the feasibility of long-term maintenance depends on patients remaining fit for extended therapy.

Critically, the de-escalation principle is not simply a tolerability tactic but also a mechanistic and strategic hypothesis. If durable control can be achieved through immune mediated mechanisms supported by anti-angiogenic modulation, then chemotherapy might shift from serving as the primary cytotoxic engine to a role as a limited, time-bound catalyst that facilitates an effective immune response to achieve early tumor regression. This approach was explicitly framed to test whether the hypothesis could produce strong clinical signals and to generate the biological correlates needed for a precision approach to intensity selection. Importantly, this aspect is also why the work is not interchangeable with repeating the same correlative analyses for a mature, conventional chemotherapy-heavy regimen; the clinical question and the biological context fundamentally differ when chemotherapy intensity is reduced by design.

Our regimen also fits into a broader trajectory of immunotherapy plus anti-angiogenic therapy in cervical cancer, in which encouraging activity has been observed even without chemotherapy in selected settings. For example, a prospective phase II study of sintilimab plus anlotinib demonstrated clinical activity in PD-L1 positive recurrent or metastatic cervical cancer after chemotherapy, thus supporting the biological plausibility of PD-1 blockade combined with anti-angiogenic therapy in this disease[10]. Our contribution involved integrating that immune-targeted concept into the first-line setting and testing whether chemotherapy could be minimized without loss of the strong early tumor control valued by clinicians and patients.

TLSs link the immune landscape, thus facilitating benefit from a de-escalated chemotherapy plus immune-targeted regimen

To translate de-escalation into a precision strategy, biomarkers are needed to identify the patients most likely to benefit from an immune-centered backbone. TLSs provide a compelling candidate. These organized immune niches within or adjacent to tumors reflect ongoing antigen presentation, lymphocyte recruitment, and adaptive immune activation. TLS biology has been associated with favorable prognosis and enhanced response to immune checkpoint blockade across multiple tumor types; consequently, TLSs appear to capture a functional state of the tumor immune microenvironment rather than a single molecular feature[11]. In melanoma, the presence of TLSs has been associated with improved survival and enhanced responsiveness to immunotherapy, including higher response rates and prolonged PFS, thereby providing a strong precedent for using TLSs as an immune readiness marker[12].

Quantification of TLSs in pretreatment tumor samples has demonstrated clear associations between TLS abundance and clinical outcomes in patients receiving a de-escalated chemotherapy- plus immuno-targeted regimen. Moreover, patients with higher TLS-to-tumor area ratios have been found to experience better PFS than patients with lower ratios, as well as a trend toward improved OS. On the basis of a median TLS-to-tumor area ratio cutoff of 0.0045, significantly improved PFS was observed in the high TLS group, whereas the OS difference did not reach conventional statistical significance. This pattern is important, because it suggests that TLSs might be more tightly associated with disease control and durability than with early tumor shrinkage alone, in agreement with the possibility that long-term benefit in an immune-centered regimen depends on sustained immune competence.

The clinical value of TLSs in this context is not only prognostic but also potentially predictive for an immune-maintenance strategy. In a chemotherapy-heavy approach, early tumor regression may be dominated by cytotoxic sensitivity, and immune features may be difficult to disentangle. In contrast, when chemotherapy exposure is brief, and maintenance relies on immune-targeted therapy, baseline immune organization may become a stronger determinant of whether durable control is achievable. Our findings therefore suggest a practical translational direction: TLSs could be used as part of a biomarker framework to determine which patients can safely receive reduced chemotherapy intensity and which patients might need alternative intensification strategies.

TLSs also offer an appealing bridge between pathology and precision medicine. Unlike purely genomic biomarkers, TLSs can be assessed on routine tumor tissue with standardized histopathologic and spatial criteria, and they capture a composite of immune cell types and organization that is not easily represented by single-gene assays. Conceptually, TLS assessment could be integrated with other immune contexture measures to guide treatment choices. However, the immediate implications of our work are narrower and actionable: TLSs correlated with the outcomes of our novel de-escalated regimen. This correlation should be validated prospectively in larger cohorts and in randomized designs in which chemotherapy intensity is the experimental variable.

From signal to strategy: how to test chemotherapy de-escalation with TLS-guided precision

Our initial findings generated a well-supported hypothesis but cannot yet define a new standard. The next step will be to convert the de-escalation concept into a rigorously testable clinical strategy. A randomized trial comparing de-escalated chemotherapy plus immuno-targeted therapy against a conventional chemotherapy-intense immunotherapy regimen would directly address whether decreased chemotherapy exposure preserves efficacy while improving patient-centered outcomes. The KEYNOTE-826 trial established the efficacy of immunotherapy added to standard chemotherapy, thus providing a benchmark for conventional intensity in the first-line setting[5]. A modern randomized de-escalation trial must prioritize not only PFS and OS but also cumulative toxicity, treatment delivery, and quality of life, because the core promise of de-escalation is improved net clinical benefit, not merely non-inferior tumor control.

Biomarker testing should be integrated from the outset. TLS assessment could be used in at least 2 ways: as a stratification factor to ensure balanced immune context across arms and as a candidate predictive marker for differential benefit from de-escalation. The broader literature supports the role of TLSs as immune activation hubs and a marker associated with immunotherapy responsiveness, thereby strengthening the rationale for making TLSs central rather than exploratory in future trials[11,12]. The observed association between TLSs and superior clinical outcomes on this regimen justifies prospective validation and methodological standardization of TLS quantification.

Finally, de-escalation must be contextualized according to stage and treatment intent. In locally advanced disease, immunotherapy has begun to demonstrate benefit when added to chemoradiotherapy with subsequent maintenance, yet not all strategies succeed; therefore, biomarkers and careful regimen design are necessary[7,9]. For metastatic or recurrent disease, the existence of multiple active systemic options including immunotherapy and anti-angiogenic therapy creates an opportunity to tailor intensity and sequence rather than defaulting to prolonged cytotoxic therapy for all. Evidence suggests the viability of an immune-maintenance model after brief induction

chemotherapy as one such tailored approach, wherein TLSs might help identify the patients most likely to achieve durable benefit.

Beyond using TLSs to guide patient selection, modulating TLS biology offers a compelling mechanistic avenue to solve the problem of therapeutic resistance. Resistance to immune-targeted therapies in cervical cancer is frequently driven by an acquired immunosuppressive or "cold" tumor microenvironment, where T-cell exclusion and exhaustion impair durable disease control. Because TLSs function as localized, lymph-node-like hubs for *de novo* antigen presentation, T-cell priming, and B-cell activation, actively inducing their formation might potentially reprogram this resistant niche. Emerging preclinical and translational evidence indicates that TLS-inducing strategies, such as the targeted delivery of crucial chemokines (e.g., CXCL13 and CCL19)[13,14], local administration of STING agonists, or vascular normalization *via* LIGHT (TNFSF14), successfully converts immunologically barren microenvironments into "hot" tumors, thereby restoring sensitivity to immune checkpoint blockade[15]. In the context of our de-escalation framework, patients with TLS-low tumors at baseline might otherwise face primary resistance and rapid progression. We hypothesize that integrating TLS-inducing agents or stromal modulators into the short induction phase might artificially "prime" the microenvironment, thus functionally converting TLS-low tumors into TLS-high phenotypes. This therapeutic induction of TLSs has potential to expand the proportion of patients capable of mounting sustained, localized anti-tumor immunity, and ultimately overcome resistance and broaden the applicability of chemotherapy-free maintenance strategies.

Conclusions

The field of cervical cancer therapy is entering an era in which immuno-targeted combinations can deliver meaningful survival improvements, but the next leap will require optimizing treatment intensity rather than only adding agents. Large trials have already demonstrated that targeted therapy and immune checkpoint blockade improve outcomes when they are layered onto standard chemotherapy to treat advanced disease, and have also shown that immunotherapy can add benefit to chemoradiotherapy in high-risk locally advanced disease. These successes create the proper conditions to formally test whether chemotherapy can be decreased without sacrificing efficacy when an effective immuno-targeted backbone is deployed early.

This strategy establishes a concrete starting point by demonstrating that only 2 cycles of induction chemotherapy combined with penpulimab and anlotinib, followed by chemotherapy-free maintenance, can generate high response rates and encouraging survival signals in advanced cervical cancer. The primary novelty is the deliberate decrease in chemotherapy intensity, thereby reframing chemotherapy as a limited initiator rather than an extended scaffold. The second key message is that TLSs correlate with benefit on this novel regimen, and link the immune landscape to the feasibility of an immune-centered maintenance strategy. Together, these 2 features outline future directions for precision therapy: de-escalation is most feasible when paired with biomarkers that identify patients in whom immune mediated control is biologically plausible.

In the future, the most important work will be prospective and comparative. Randomized trials that explicitly test reduced chemotherapy exposure, alongside standardized TLS assessment and integrated translational endpoints, are required to determine whether de-escalation enhances net benefit and to define how to tailor intensity for individual patients. TLSs have a strong biological foundation as markers of organized anti-tumor immunity and immunotherapy responsiveness, and therefore are particularly relevant when chemotherapy is minimized, and maintenance relies on sustained immune engagement. If validated, TLS-guided de-escalation could potentially provide a practical embodiment of precision cervical cancer therapy, aligning clinical benefit with a more sustainable treatment burden.

Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Shengtao Zhou.
Wrote the paper: Bohao Zheng, Dian Fan.

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Cite this article as: Zheng B, Fan D, Zhou S. Less is more: patients with cervical cancer benefit from de-escalated chemotherapy plus immuno-targeted therapies. Cancer Biol Med. 2026; 23: 1051-1056. doi: 10.20892/j.issn.2095-3941.2026.0139