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Transformative clinical trials in gynecologic radiation oncology in 2023–2024: Shaping modern treatment practices

Mémoire présenté par :
Docteur El AYACHI Zineb
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Dr. Touria BOUHAFA
Oncologue

Transformative clinical trials in gynaecologic radiation oncology in 2023-2024: Shaping modern treatment practices

Essais cliniques majeurs en radiothérapie gynécologique : 2023-2024

ABSTRACT

The field of gynaecologic oncology has evolved rapidly in recent years, largely driven by advances in both radiotherapy and systemic therapies. These innovations have reshaped the management of key gynaecologic cancers, including cervical, endometrial, vaginal, and vulvar cancers, leading to more personalized and effective treatment approaches. This review explores pivotal clinical trials conducted between 2023 and 2024 that have potentially modified current practices. Through an extensive analysis of randomized controlled trials and meta-analyses, we examine the evolving role of radiotherapy, the integration and sequencing of immunotherapy, and the refinement of neoadjuvant and adjuvant treatments based on molecular classifications. The combination of immunotherapy with chemoradiotherapy has shown promising outcomes, particularly in patients with locally advanced cervical cancer. For endometrial cancer, molecular profiling has enabled a more precise classification of tumour sub-types, leading to better-targeted adjuvant therapies that reduce unnecessary interventions and increase treatment efficacy. In parallel, radiotherapy has advanced with the increasing use of modern techniques such as intensity-modulated radiotherapy and more recently the developments of adaptive treatments in order to minimize

exposure to healthy tissue, thereby reducing toxicity and enhancing patient quality of life. Integration of image-guided brachytherapy and expansion of capabilities with newer generation of brachytherapy applicators have also increased possibilities to achieve efficient local treatments, including in very advanced cases. However, despite progress in common gynaecologic cancers, the management of rare cancers such as vulvar and vaginal cancers continues to face challenges due to limited clinical research and treatment data. This review highlights the transformative potential of these innovations and emphasizes the need for continued research and personalized treatment strategies to optimize patient outcomes in gynaecologic oncology.

RÉSUMÉ

Le domaine de l'oncologie gynécologique a évolué rapidement ces dernières années, en grande partie grâce aux progrès de la radiothérapie et des thérapies systémiques. Ces innovations ont remodelé la prise en charge des principaux cancers gynécologiques, notamment les cancers du col de l'utérus, de l'endomètre, du vagin et de la vulve, conduisant à des approches thérapeutiques plus personnalisées et plus efficaces. Cette revue explore les essais cliniques pivots menés entre 2023 et 2024 qui ont potentiellement modifié les pratiques actuelles. Par une analyse approfondie des essais contrôlés randomisés et des méta-analyses, nous examinons le rôle évolutif de la radiothérapie, l'intégration et le séquenc¸ age de l'immunothérapie et le perfectionnement des traitements néoadjuvants et adjuvants basés sur des classifications moléculaires. L'association de l'immunothérapie et de la chimioradiothérapie a montré des résultats prometteurs, en particulier chez les patientes atteintes d'un cancer du col de l'utérus localement évolué. Pour le cancer de l'endomètre, le profilage moléculaire a permis une classification plus précise des sous-types de tumeurs, conduisant à des thérapies adjuvantes mieux ciblées qui réduisent les traitements inutiles et augmentent l'efficacité des prises en charge. Parallèlement, la radiothérapie a progressé avec l'utilisation croissante de techniques modernes telles que la radiothérapie avec modulation d'intensité et plus récemment le développement de traitements adaptatifs afin de minimiser l'exposition des tissus sains, réduisant ainsi la toxicité et améliorant potentiellement la qualité de vie des patientes. L'intégration de la curiethérapie guidée par l'image et l'expansion

des capacités avec une nouvelle génération d'applicateurs de curiethérapie ont également augmenté les possibilités de réaliser des traitements locaux efficaces, y compris dans les cas très avancés. Cependant, malgré les progrès réalisés dans les cancers gynécologiques les plus fréquents, la prise en charge des cancers rares tels que les cancers de la vulve et du vagin continue de faire face à des défis en raison d'un accès insuffisant à la recherche clinique et de données de traitement limitées. Cette revue met en évidence le potentiel transformateur de ces innovations et souligne la nécessité de poursuivre la recherche et de mettre en place des stratégies de traitement personnalisées pour optimiser les résultats des traitements en oncologie gynécologique.

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I. Introduction

Over the past decade, the field of gynaecologic oncology has witnessed remarkable progress, fundamentally altering our understanding and management of these cancers. This transformative period has not only enhanced diagnostic and therapeutic capabilities but also introduced groundbreaking innovations in research and clinical practice, paving the way for more effective treatments. Concurrently, the indications and techniques of radiotherapy have evolved drastically, integrating cutting-edge technologies and evidence-based strategies.

Breakthroughs in systemic therapies, including the development of innovative approaches like immunotherapy combinations and neoadjuvant treatments, have significantly transformed the standard treatment protocols for gynaecological cancers. These advancements have reshaped clinical practices and approaches for cancers such as endometrial, cervical, vaginal, and vulvar cancers, where radiation therapy continues to play a major role in the comprehensive management of these malignancies.

This work highlights the cutting-edge research that has driven these groundbreaking innovations, placing a strong emphasis on how deeper and more comprehensive insights into the molecular and genetic foundations of gynaecologic cancers are paving the way for more effective and highly personalized treatment strategies. By exploring the latest studies, clinical trials, and scientific breakthroughs, this work seeks to illustrate the transformative potential of these advancements in improving patient outcomes and shaping the future of gynaecologic cancer care.

II. Materials and methods

We conducted an extensive and detailed search of the Medline database spanning the years 2023 to 2024, using the search engine PubMed to identify relevant studies. Our inclusion criteria focused on randomized trials and meta-analyses pertinent to the field of radiotherapy in patients diagnosed with gynaecologic cancers. To ensure a systematic and comprehensive review, our search strategy incorporated specifically curated keywords that encompassed a range of gynaecologic malignancies and treatment modalities. These terms were carefully selected to maximize the capture of pertinent studies and included phrases such as: “Radiotherapy and cervical cancer,” “Radiotherapy and endometrial cancer,” “Immunotherapy and gynaecologic cancers,” and “Targeted therapy and gynaecologic cancers.” The inclusion of these precise terms allowed us to conduct a thorough examination of the most recent research in this domain.

In addition to the PubMed search, we expanded our review by including studies presented at major international conferences renowned for their significant influence on clinical practice and research in oncology. The conferences of interest included the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), the International Society of Gynaecologic Cancers (IGCS), and the European Society of Gynaecological Oncology (ESGO). Our review placed particular emphasis on randomized phase III trials for cervical and endometrial cancers, as these provide the highest level of evidence. For vulvar and vaginal cancers, which are considered rare tumours and lack randomized trials, we extended our

inclusion criteria to encompass phase II trials presented at these esteemed congresses.

The predefined inclusion criteria were meticulously applied to ensure the relevance and quality of the selected studies. Specifically, we included:

1. randomized controlled trials and meta-analyses published between 2023 and 2024.
2. studies focusing on gynecologic cancers, including cervical, endometrial, vaginal, and vulvar cancers.
3. trials presented at major international conferences (e.g., American Society of Clinical Oncology, European Society for Medical Oncology [ESMO], International Society of Gynaecologic Cancers, European Society of Gynaecological Oncology) with a focus on phase III studies for cervical and endometrial cancers and on phase II trials for vulvar and vaginal cancers

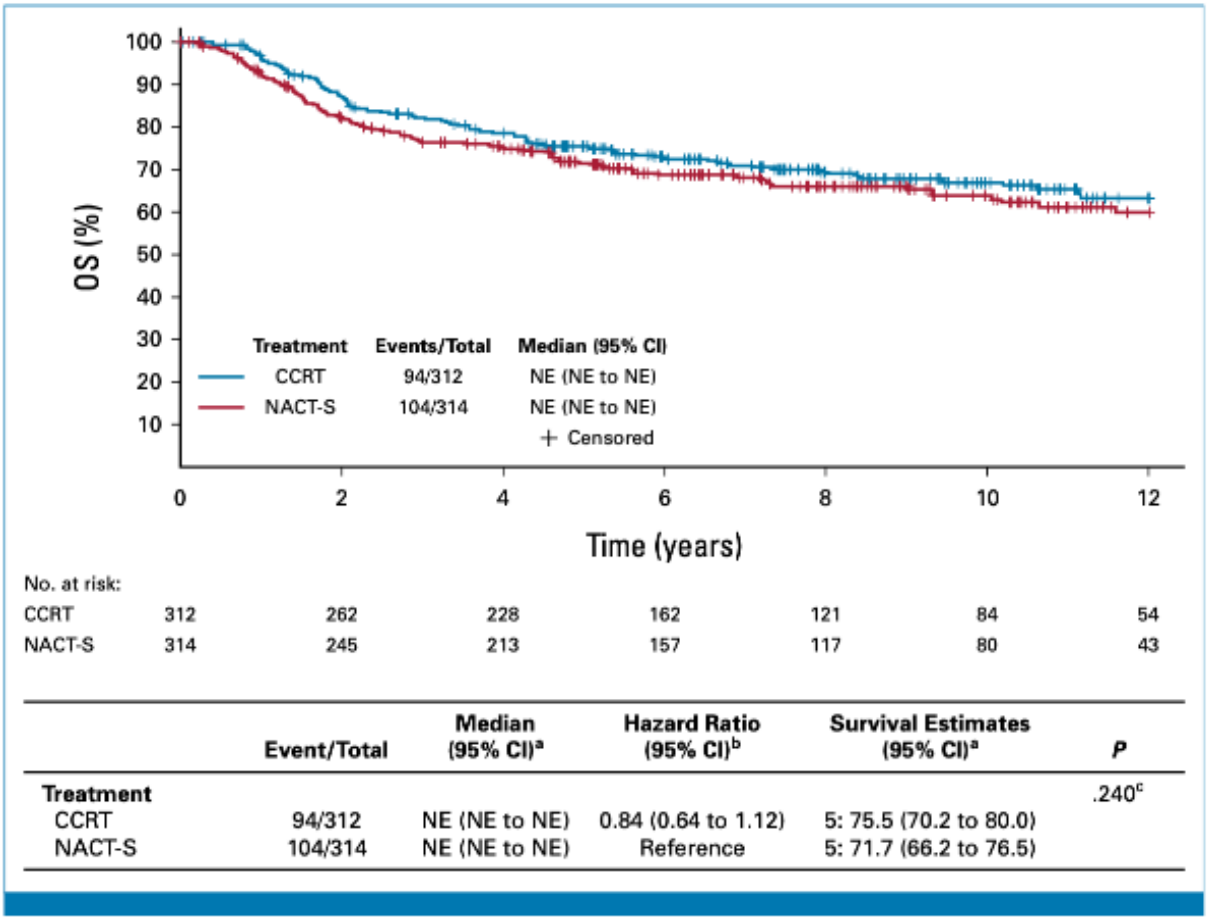
From the studies identified through our rigorous search strategy, we systematically extracted detailed information regarding trial design, population characteristics, interventions, and outcomes. For studies evaluating advanced technological aspects of treatment, such as image-guided brachytherapy, prospective cohort studies were also reviewed to provide a comprehensive understanding of the evolving therapeutic landscape. The primary focus was on progression-free survival, overall survival, and significant clinical benefits demonstrated by the interventions.

III. Cervical cancer

1. *Confirmation of the role of upfront chemoradiation followed with brachytherapy boost*

In order to resolve conflicting evidence on the value of neoadjuvant chemotherapy followed by surgery versus standard concomitant chemoradiotherapy for patients with stage IB2- IIB cervical carcinoma, the European Organization for Research and Treatment of Cancer (EORTC) Gynaecological Cancer Group recently published the results of EORTC-55994, a multicentre trial comparing neoadjuvant chemotherapy followed by surgery with the standard approach of chemoradiotherapy for patients with stage IB2-IIB cervical cancer. The study included 626 patients who were randomly assigned to either receiving neoadjuvant chemotherapy followed by surgery (designated as "NACT-S group" or "NACT-S arm", 314 patients) or chemoradiotherapy (designated as "CRT group" or "CRT arm", 312 patients). The main goal was to compare the 5-year overall survival rates between the two treatment strategies. After a median follow-up of 8.7 years, the trial found that the 5-year overall survival rates were similar between the two groups, with 72 % in the NACT-S group and 76 % in the CRT group, showing no significant difference **(Figure 1)**. Secondary outcomes, such as progression-free survival, treatment-related toxicity, and health-related quality of life, were also analyzed. The completion rates for the assigned treatments were slightly higher in the CRT group (82 %) compared to the NACT-S group (71 %). Short-term severe adverse events (grade 3 or higher) were more common in the neoadjuvant chemotherapy followed by surgery -S group (41 % ver- sus 23%

in the CRT group), while long-term severe adverse events were more frequent in the CRT group (21 % versus 15 % in the NACT- S group). Ultimately, the trial did not demonstrate a clear advantage of neoadjuvant chemotherapy followed by surgery over chemoradiotherapy in terms of overall survival. The 5-year progression-free survival rate was 57 % in the NACT-S arm compared with 66 % in the CRT arm (hazard ratio [HR]: 0.73; 95 % confidence interval [95 % CI]: 0.57-0.93; P = 0.011). In addition to this significant superiority of chemoradiotherapy over neoadjuvant chemotherapy followed by surgery in terms of progression-free survival, adjuvant radiotherapy with or without concurrent chemotherapy was given postoperatively to 48 % of patients in the NACT-S arm who completed their protocol treatment for reasons of positive nodes, parametrial infiltration, or positive surgical margins [1]. This study therefore confirmed previous data obtained few years earlier from another randomized trial and showing that cisplatin-based chemoradiotherapy resulted in superior disease-free survival compared with neoadjuvant chemotherapy followed by surgery for locally advanced cervical cancer [2]. Up to 2023, the standard of care for a locally advanced cervical cancer is therefore chemoradiation followed with brachytherapy boost, as per European Guidelines [3].



	Event/Total	Median (95% CI)[a]	Hazard Ratio (95% CI)[b]	Survival Estimates (95% CI)[a]	*P*
Treatment					.240[c]
CCRT	94/312	NE (NE to NE)	0.84 (0.64 to 1.12)	5: 75.5 (70.2 to 80.0)	
NACT-S	104/314	NE (NE to NE)	Reference	5: 71.7 (66.2 to 76.5)	

Figure 1: Overall Survival Analysis for Neoadjuvant Chemotherapy Followed by Surgery vs. Chemoradiation in Cervical Cancer (EORTC-55994).

The EMBRACE study established MRI-guided brachytherapy as the optimum technique to increase the dose to targets volume while minimizing doses to organs at risk. This study reported improved local control compared to previous techniques based on 2D brachytherapy [4]. In a meta-analysis of studies assessing the effects of point-A and volume-based brachytherapy, superior outcome was reported with volume-based brachytherapy. The 3-year disease-free survival for point-A and volume-based studies were 67 % (95 % CI: 60 %-73 %) and 79 % (95 % CI: 76 %-82 %) respectively (P = 0.001). Three-

year local control for point-A and volume-based studies were 86 % (95%CI:81%-90%) and 92%(95%CI:91%-94%) respectively (P = 0.01) [5] **(Figure 2)**. Analyses from EMBRACE data led to refining criteria for a high-quality treatment and the European Society of Gynaecological Oncology (ESGO) and the European Society for Radiotherapy and Oncology (ESTRO) established in 2024 a list of quality indicators for radiation therapy in cervical cancer [6]. These guidelines require that all treatment decisions involve a team of specialists, including gynaecologic oncologists, radiologists, and radiation oncologists, to develop a comprehensive and tailored treatment plan for each patient. An essential component of this process is a thorough pretreatment evaluation, which includes advanced imaging techniques such as pelvic MRI and positron-emission tomography (PET)-CT scans to accurately stage the disease and guide treatment. Timely initiation of radiotherapy is also critical, with specific timelines set to minimize delays that could compromise treatment effectiveness. The use of intensity- modulated radiotherapy is considered as the standard of care to reduce radiation exposure to healthy tissues, thereby lowering the risk of treatment-related side effects. Additionally, daily image- guided radiotherapy with individualized margins is required to maintain precise targeting of the tumour, accounting for any internal movement. Brachytherapy use plays a significant role in these criteria, as a prerequisite for high quality treatment. In advanced cases, a combination of intracavitary and interstitial brachytherapy is recommended to ensure effective dose distribution. The over-all treatment time is also a crucial factor, with an objective to complete treatment preferably within 50 days and not

exceeding 56 days to avoid tumour repopulation and increase cure rates. These indicators aim at standardizing treatment protocols and optimize patient outcomes by focusing on factors such as treatment planning, dose optimization, and quality assurance. They may serve as a benchmark for healthcare professionals, promoting best practices and enhancing the overall quality of care and should also serve as essential criteria when performing trials integrating systemic therapies [6].

Beyond local control, which has now reached very high rates, a significant challenge is now to decrease distant failure probability and several studies addressing the role of systemic intensification in advanced cervical cancer (including immune checkpoint inhibitors and chemotherapy) became available in 2023 and 2024.

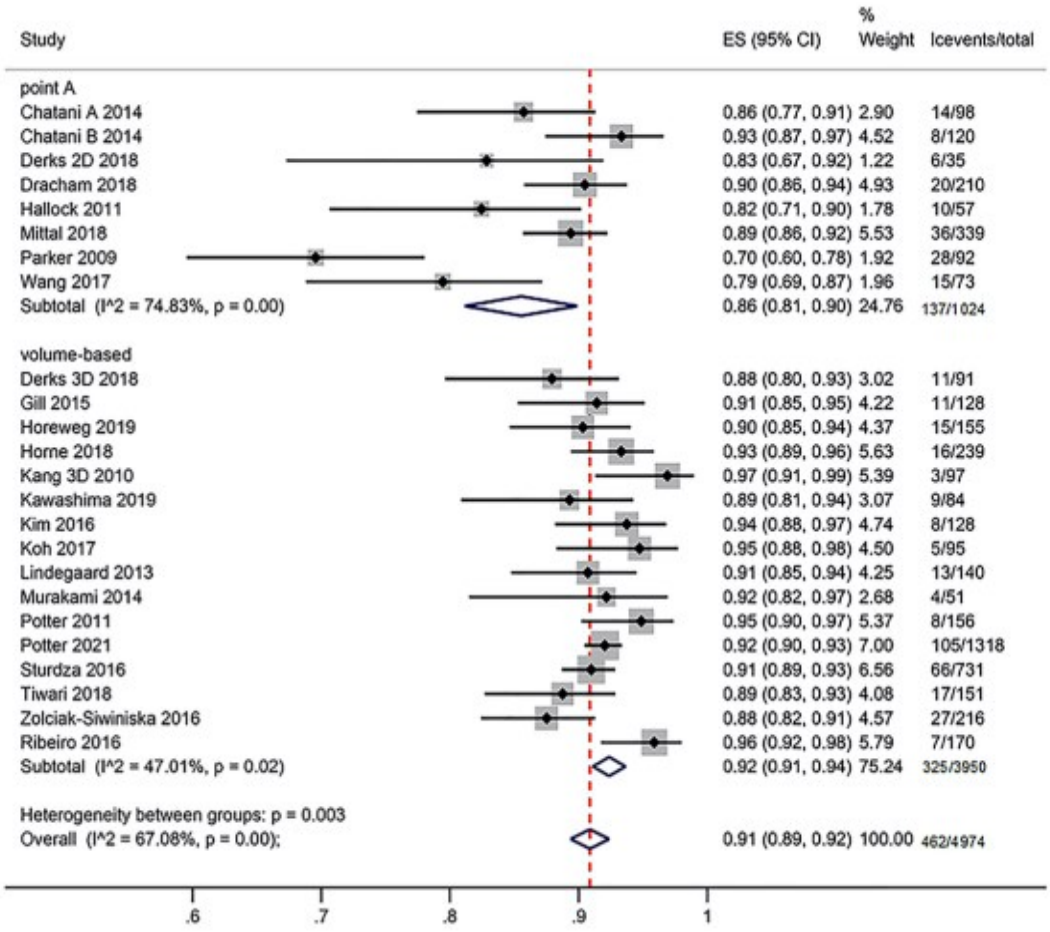


Figure 2: Forest Plot showing 3-year local control between point-A studies and volume-based studies I^2: Heterogeneity ES = Estimate Size 95% CI = 95% Confidence Interval.

2. *Increasing role of immunotherapy*

Combining radiotherapy with immune checkpoint inhibitors has shown promise in enhancing therapeutic effects [7,8]. Immune checkpoint inhibition, which consists of pharmaceutical modulation of inhibitory signals suppressing T-cell activation, has been a focal point of these studies. The CALLA trial, a multicentre, randomized, double-blind, placebo-controlled phase III study, evaluated the efficacy of adding program death ligand (PD-L)-1 inhibitor durvalumab to standard chemoradiotherapy for patients with locally advanced cervical cancer [9] **(Table 1)**. The trial was negative and did not meet its primary endpoint; progression-free survival for patients treated with durvalumab in combination with chemoradiotherapy compared with placebo in combination with chemoradiotherapy in the intention-to-treat population did not differ significantly, concluding that addition of durvalumab to chemoradiotherapy did not significantly improve progression-free survival compared to standard treatment alone **(Figure 3)**. At data cutoff, median progression-free survival had not been reached for either group (HR: 0.84; 95 % CI: 0.65–1.08; P = 0.17); 12-month progression-free survival rate was 76.0 % (95 % CI: 71.3–80.0 %) with durvalumab and 73.3 % (95 % CI: 68.4–77.5 %) with a placebo. However, while durvalumab did not significantly improve progression-free survival, these negative results highlight the role of biomarkers to guide systemic intensification and identify predictive factors of activity in the field of radio-immunotherapy combinations. Indeed, an exploratory post hoc analysis suggested a progression-free survival benefit in the durvalumab group versus the placebo group observed starting at tumor PD-L1 tumor area positivity

score 20 % or greater. It is however a clinical challenge to use biomarkers due to very high rate of PDL-1 positivity observed in this trial; because when the CALL trial was designed, there was no evidence to suggest that PD-L1 was a significant biomarker for locally advanced cervical cancer. Consequently, the study was designed to include an all-comer population. In addition, progression-free survival results in CALLA trial were relatively low despite exclusion of patients with higher disease burden and prognostic factors for poorer outcomes; such as patients with para-aortic lymph node extension (2-years progression-free survival rate: 62.1 % for placebo plus chemoradiotherapy and 65.9 % for durvalumab plus chemoradiotherapy). In the study, approximately 38 % of patients had point A-directed brachytherapy, questioning the quality of brachytherapy techniques and introducing a major bias in the data analysis.

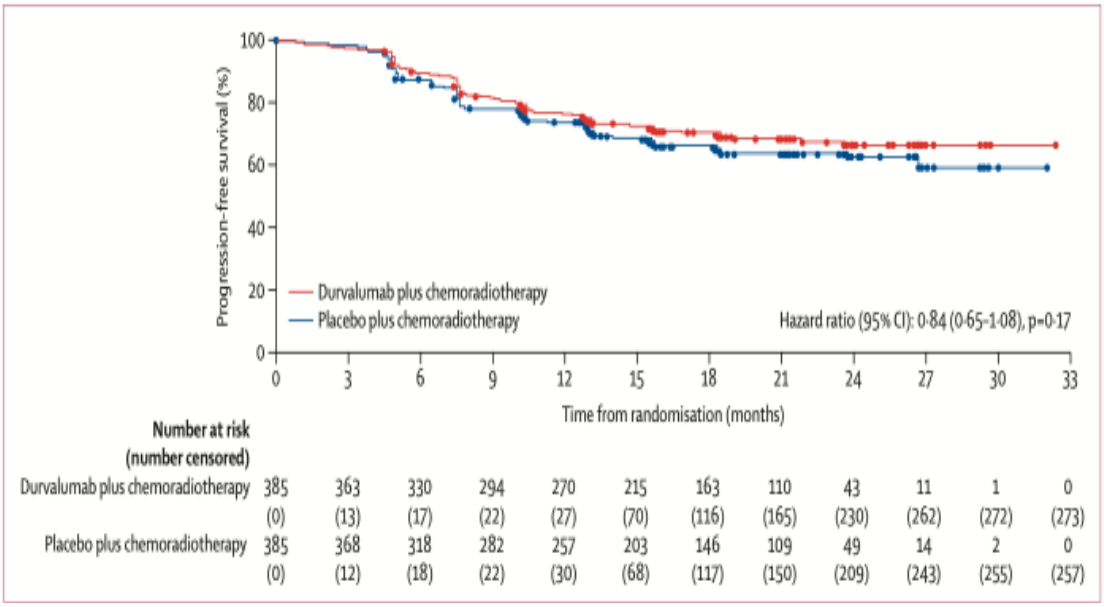


Figure 3: Kaplan-Meier plot of progression-free survival for Durvalumab plus chemoradiotherapy versus placebo plus chemoradiotherapy (CALLA trial)

More recently, the KEYNOTE A-18 trial, a pivotal phase III clinical study, assessed the efficacy of pembrolizumab, an inhibitor of programmed cell death 1 (PD-1) receptor, combined with standard chemoradiotherapy for locally advanced cervical cancer. This trial demonstrated a statistically significant and clinically meaningful improvement in progression-free survival. Progression-free survival rates at 24months were 68 % in the group receiving pembrolizumab and chemoradiotherapy versus 57 % in the group receiving the placebo and chemoradiotherapy **(Figure 4)**. The hazard ratio for disease progression or death was 0.70 (95 % CI: 0.55–0.89, P = 0.0020), meeting the protocol-specified primary objective with a favorable trend in overall survival rate (87 % in the pembrolizumab-CRT group versus 81 % in the placebo-CRT group at 24 months) [10]. These results suggested that pembrolizumab could potentially become a new standard of care, which led to an approval by the Food and Drug Administration (FDA) for treating stage III-IV cervical cancer, defined according to the International Federation of Gynaecology and Obstetrics (FIGO) 2014 staging system (referring to tumours extending to pelvic sidewall or hydronephrosis/non-functioning kidney or extension to lower vagina or beyond the true pelvis to adjacent pelvic organs). In preplanned stratified analysis IB2-IIB node positive did not have any benefit. There was a detriment in age greater than 65 years and benefit was in patients where intensity-modulated radiotherapy was used. There were concerns on treatment parameters, with more than 25 % of patients having extended overall treatment time and only 22 % of interstitial brachytherapy in this advanced population. Despite other limitations such as the lack of systematic (^{18}F)-

fluorodeoxyglucose PET/CT scans, pembrolizumab showed major potential. Survival analysis showed a significant overall survival benefit with the addition of pembrolizumab over standard chemoradiotherapy. Three-year overall survival rate was 82.6 % (95 % CI: 78.4–86.1 %) in the group receiving the pembrolizumab and chemoradiotherapy and 74.8 % (95 % CI: 70.1–78.8 %) in the group receiving the placebo and chemoradiotherapy. The hazard ratio for death was 0.67 (95 % CI: 0.50–0.90; P = 0.0040), meeting the protocol-specified primary objective [10]. Based on these results that suggest a potential role for the addition of pembrolizumab to chemoradiotherapy for treatment of newly diagnosed, high-risk, locally advanced cervical cancer, evaluation by French health authorities is pending for advanced stage cervical cancer. Cost-benefit analyses and identification of biomarkers to guide treatment strategy are still required and crucial to analyse the true plus-value of immunotherapy at a broader population scale, especially in high incidence regions.

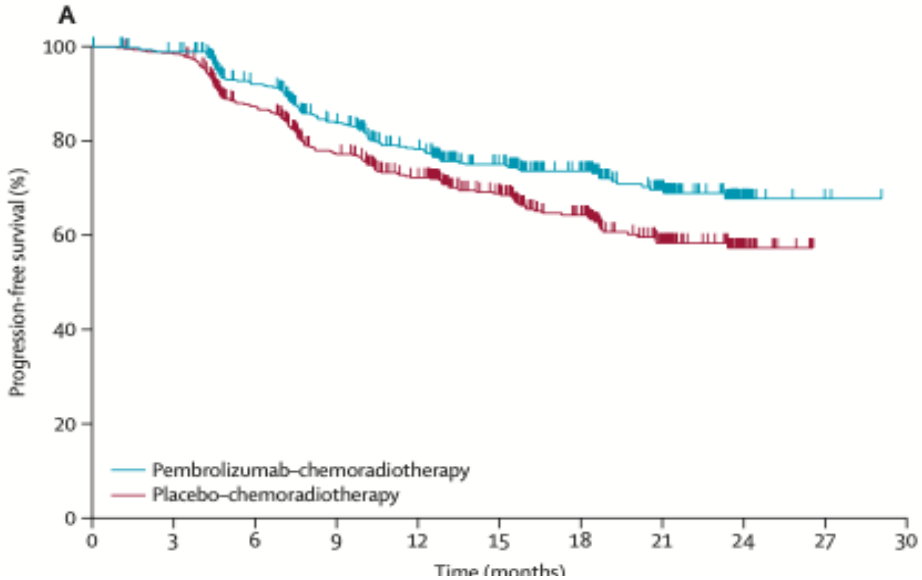


Figure 4: Kaplan-Meier estimates of progression-free survival for Pembrolizumab plus chemoradiotherapy versus placebo plus chemoradiotherapy (KEYNOTE A-18)

3. Refining the role of chemotherapy

Adjuvant and neoadjuvant chemotherapy have also been explored to enhance patient outcomes, particularly in reducing disease recurrence and mortality due to distant metastases. The OUTBACK randomized phase III trial evaluated the efficacy of adjuvant chemotherapy following standard chemoradiotherapy. 926 patients were enrolled and randomly assigned to receive standard cisplatin-based chemoradiotherapy or standard cisplatin-based chemoradiotherapy followed by adjuvant chemotherapy with four cycles of carboplatin and paclitaxel. The primary endpoint was overall survival at 5 years. The study was negative and no significant improvement in overall survival was found compared to standard follow-up care alone (5-year overall survival was 72% (95% CI 67 to 76; 105 deaths) in the adjuvant chemotherapy group versus 71% (66 to 75; 116 deaths) in the chemoradiotherapy only group (difference 1% [95% CI -6 to 7]; HR 0·90 [95% CI 0·70 to 1·17]; p=0·81). Concerning safety results, the most frequently observed clinically significant grade 3-4 adverse events included neutropenia, reported in 71 patients (20%) in the adjuvant chemotherapy group compared to 34 patients (8%) in the chemoradiotherapy-only group, and anemia, occurring in 66 patients (18%) versus 34 patients (8%), respectively. Serious adverse events were documented in 107 patients (30%) in the adjuvant chemotherapy group and 98 patients (22%) in the chemoradiotherapy-only group, with infectious complications being the most common cause [11].Therefore, Adjuvant carboplatin and paclitaxel chemotherapy given after standard cisplatin-based chemoradiotherapy for unselected locally advanced cervical cancer has been

abandoned outside a clinical trial as it increased short-term toxicity and did not improve overall survival. OUTBACK trial excluded patients with FIGO-2018 stage IIIC2 cervical cancer (para-aortic extension), which limits the relevance of the results for those very high-risk patients. Additionally, the open-label design could introduce bias in reporting and assessment of outcomes. Furthermore, the lack of systematic PET/CT scans as a systematic pre-treatment modality could lead to inaccurate staging and monitoring of disease progression. Lastly, while the intention-to-treat analysis is robust, it might not fully account for protocol adherence [11]. In a meta-analysis of adjuvant chemotherapy including OUTBACK, pooled hazard ratios for overall and progression-free survival were 0.78 (95 % CI: 0.45–1.33, P = 0.36) and 0.85 (95 % CI: 0.65–1.10, P = 0.22), respectively [13].

More recently, the INTERLACE trial [12] investigated the potential benefits of induction chemotherapy (6 weeks of carboplatin/paclitaxel) followed by chemoradiotherapy. This randomized, controlled study involved 32 centers across five countries and focused on whether short-course weekly induction chemotherapy before standard chemoradiotherapy could improve progression-free and overall survival. 500 eligible patients were enrolled and randomly assigned to the chemoradiotherapy alone group (n=250) or the induction chemotherapy with chemoradiotherapy group. Primary endpoints were progression-free survival and overall survival. The trial reported significant improvements in both endpoints, particularly for patients with node-negative disease; 5-year progression-free survival rate was 73 % with induction chemotherapy and chemoradiotherapy and 64 % with

chemoradiotherapy alone (HR: 0.65; 95 % CI: 0.46–0.91, P = 0.013). The corresponding 5-year overall survival rates were 80 % and 72 % (HR: 0.61; 95% CI: 0.40–0.91; P = 0.04) **(Figure 5).** Though offer encouraging prospects, indirect comparison with EMBRACE data suggests underperformance of the standard arm, that may have an impact on survival data [14]. The INTERLACE trial represents the first published substantial overall survival improvement among patients with locally advanced cervical cancer since concomitant cisplatin over two decades ago, but it must be highlighted that it comes with several potential limitations, as the study enrolment extended over more than ten years, leading to variations in the treatment protocols and techniques used over time, which may contribute to relatively high local relapses rates. In addition, almost 60 % of patients had a N0 tumor, which might restrict the applicability of the results to broader populations. Authors, however, anticipate that para-aortic node positive patients would also benefit from induction chemotherapy with chemoradiotherapy as a single centre retrospective review of para-aortic node-positive patients treated with INTERLACE protocol induction chemotherapy and extended field chemoradiotherapy confirmed 3-year overall survival and progression-free survival rates (83% and 78%) [15].

Such strategy may offer a valuable addition to standard of care, especially where institutions are facing prolonged waiting times with a limited access to advanced brachytherapy techniques. Publication of quality-of-life data is also awaited.

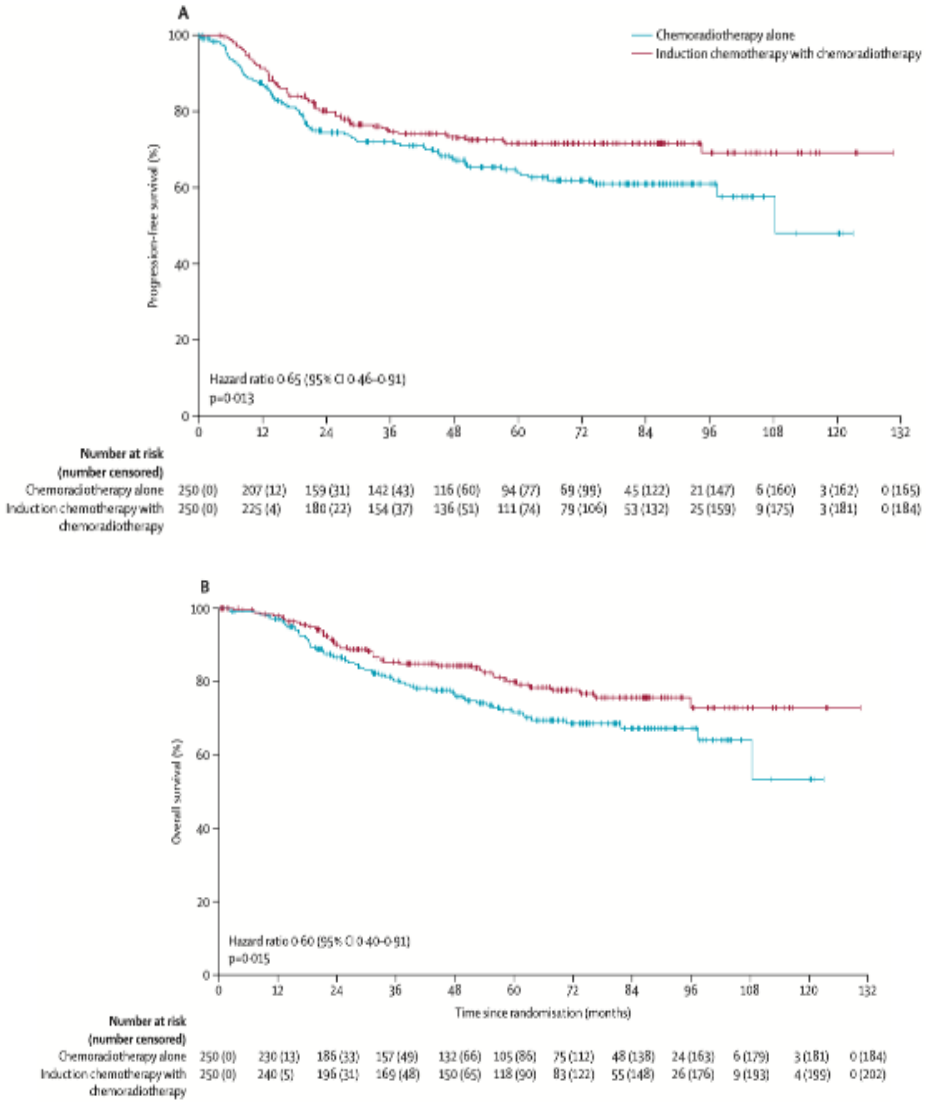


Figure 5: Kaplan-Meier estimates of progression-free survival (A) and overall survival (B) for Chemoradiotherapy alone versus induction chemotherapy with chemoradiotherapy in patients with locally advanced cervical cancer (INTERLACE)

4. Optimal technique for adjuvant radiotherapy

While the benefit of radiotherapy in treating cervical cancer with intermediate or high-risk factors is well-established, determining the most optimal technique for minimizing toxicity remains crucial. In 2021, the randomized phase III PARCER trial demonstrated with a high level of evidence that postoperative radiotherapy conducted through an intensity-modulated radiotherapy technique produced less grade ≥2 late gastrointestinal toxicity, compared to three-dimensional (3D) conformal radiotherapy, without any deleterious impact in terms of disease control (the 3-year cumulative incidence of grade ≥2 late GI toxicity in the IG-IMRT and 3D-CRT arms were 21.1% versus 42.4% (hazard ratio [HR] 0.46; 95% CI, 0.29 to 0.73; P < .001), at a median follow up of 46 months [16] **(Table 2)**. Moreover, no difference was observed in Progression free survival, Disease free survival, and Overall survival at 3 and 5 years. In summary, the findings of the PARCER trial in cervical cancer patients indicate that postoperative IG-IMRT is associated with a reduced incidence of late toxicity compared to conventional 3D-CRT, while maintaining equivalent efficacy outcomes. Therefore, IG-IMRT should be considered the radiotherapy technique of choice for this patient group. Simultaneous bowel and marrow sparing techniques need to be further developed, as the focus was on bowel sparing but none marrow sparing was prospectively studied [16].

More recently, the financial aspects of intensity-modulated radiotherapy in this context were analyze and published in 2024. Higher initial costs of image-guided, intensity-modulated radiotherapy were shown, but the yearly financial impact per patient was significantly higher for 3D-

chemoradiotherapy compared with image-guided, intensity-modulated radiotherapy [17]. This analysis confirmed the societal benefit of modern radiotherapy techniques that should be employed to decrease morbidity rates and improve patient outcome. Though this trial was performed in the adjuvant setting, together with previously published small phase III randomized trials, image-guided, intensity-modulated radiotherapy should be considered standard approach. Previously discussed limitations of INTERLACE trials highlight the role of relevant quality assurance program within the clinical trials testing drugs in combination with radiotherapy in the field.

	Grade ≥ 2 Toxicity			Grade ≥ 3 Toxicity		
Adverse Event	IG-IMRT (n = 151), No. (%)	3D-CRT (n = 149), No. (%)	P	IG-IMRT (n = 151), No. (%)	3D-CRT (n = 149), No. (%)	P
Diarrhea	6 (3.9)	11 (7.4)	.20	2 (1.3)	4 (2.6)	.44
Anorexia	1 (0.6)	10 (6.7)	.005	0 (0)	1 (0.6)	.50
Nausea	1 (0.6)	3 (2.0)	.37	0 (0)	0 (0)	NA
Vomiting	2 (1.3)	7 (4.7)	.10	0 (0)	0 (0)	NA
Abdominal bloating	20 (13.2)	39 (26.2)	.006	2 (1.3)	1 (0.6)	1.0
Abdominal pain	16 (10.5)	22 (14.8)	.27	0 (0)	4 (2.6)	.06
Malabsorption	2 (1.3)	2 (1.3)	1.0	0 (0)	0 (0)	NA
Bowel perforation	1 (0.6)	2 (1.3)	.62	1 (0.6)	2 (1.3)	.62
Bowel obstruction	1 (0.6)	8 (5.3)	.01	1 (0.6)	8 (5.3)	.02
GI stricture	0 (0)	0 (0)	.49	0 (0.0)	1 (0.6)	.50
Rectal bleeding	2 (1.3)	5 (3.4)	.28	1 (0.6)	2 (1.3)	.62
Cystitis	8 (5.3)	9 (6)	.78	2 (1.3)	2 (1.3)	1.0
Urinary frequency	3 (1.9)	6 (4.0)	.33	1 (0.6)	0 (0)	1.0
Urinary incontinence	1 (0.6)	3 (2.0)	.37	0 (0)	1 (0.6)	.50
Bladder spasms	0 (0.0)	2 (1.3)	.25	0 (0)	0 (0)	NA
Urinary fistula	0 (0.0)	0 (0.0)	NA	0 (0)	0 (0)	NA
Induration or fibrosis	0 (0.0)	5 (3.4)	.03	0 (0)	1 (0.6)	.50
Lymphedema	2 (1.3)	2 (1.3)	1.0	0 (0)	0 (0)	NA
Vaginal stenosis	2 (1.3)	8 (5.3)	.06	0 (0)	0 (0)	NA
Fatigue	7 (4.6)	20 (13.4)	.008	0 (0)	1 (0.6)	.50
Constitutional symptoms	3 (1.9)	11 (7.4)	.03	0 (0)	2 (1.3)	.24
Any GI toxicity	29 (19.2)	54 (36.2)	.004	5 (3.3)	20 (13.4)	.002
Any GU toxicity	9 (6)	15 (10.1)	.42	2 (1.3)	3 (2)	.68
Any GI toxicity or GU toxicity	34 (22.5)	59 (39.6)	.001	7 (4.6)	22 (14.7)	.003
Any late toxicity	37 (24.5)	61 (40.9)	.002	7 (4.6)	22 (14.7)	.003

Table 2: Late Adverse Events in the IG-IMRT and 3D-CRT Arms (PARCER trial)

IV. Endometrial cancer

1. Refining adjuvant treatments based on molecular classification

Significant advancements in endometrial cancer treatment consisted in a more accurate risk stratification based on a thorough analysis of The Cancer Genome Atlas (TCGA) research project and reshaping the therapeutic management of endometrial cancer [18]. Derived from the TCGA project, the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) approach has identified four subgroups that are now used for refining adjuvant treatments indications: 1/POLE mutated;2/mismatch repair deficient (MMRd); 3/P53 abnormal; and 4/non-specific molecular profile (NSMP) or p53 wild type tumours [19].

Each tumour subtype exhibits unique molecular and pathological characteristics, which have been associated to notable variations in clinical outcomes **(Figure 6)**. Therefore, proper subtype classification is crucial for selecting appropriate adjuvant therapy. This stratification system is now widely used, with adjuvant treatments based on specific genetic tumour profiles. Based on this classification framework, the 2023 FIGO update further refines staging by integrating these molecular subgroups into its revised criteria. The most notable changes include the integration of molecular classifications, such as POLE mutations (POLEmut) and p53 abnormalities (p53abn), which are now used to refine staging and prognostication in stage I and II tumours [20]. The update also includes more historical prognostic factors such as histological type, tumour grade, and lymphovascular space invasion, to better assess the cancer's aggressiveness. Additionally, stages III and IV have been subdivided

based on the location and size of metastatic disease, allowing for more precise categorization.

These revisions aim to improve the accuracy of staging, guide personalized treatment strategies, and enhance data collection for future research. Application of the molecular classification can avoid overtreating patients with POLEmut tumours but also identify those patients for whom intensification is required because of poor prognosis, based on P53mut profile. However, the possibility of double classifiers does exist, and the prognosis is driven by POLE mutation. This molecular classification should help us to advance both clinical management and re-search for EC, as has been achieved with subtype-specific approaches to other malignancies over the last several years; as it brings new dimensions and quality standards in pathology reporting should be adjusted worldwide. In addition, the impact of this molecular profile on survival outcome and financial burden should be assessed.

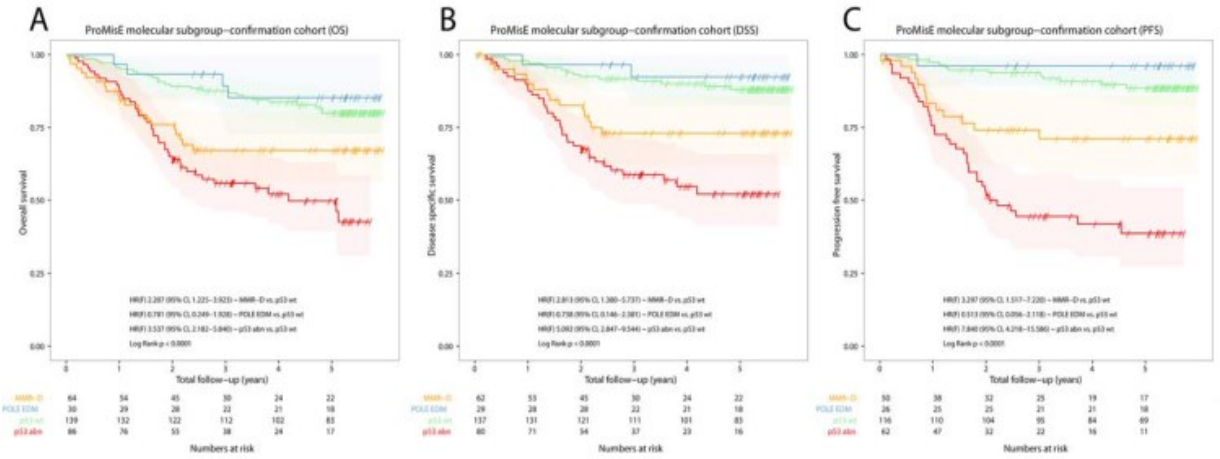


Figure 6: Kaplan–Meier survival analyses according to Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) molecular subgroups, including (A) overall survival (OS), (B) disease-specific survival (DSS), and (C) progression-free survival (PFS)

2. Adjuvant radiotherapy and molecular profiling

Prospective studies have increasingly focused on the role of adjuvant radiotherapy, particularly in the context of molecular profiling. An analysis of two major trials explored the predictive value of molecular classification in determining the response to radiotherapy in early-stage endometrioid endometrial cancer [21]. Using data from the PORTEC-1 and PORTEC-2 trials, which compared radiotherapy to surveillance and radiotherapy to vaginal brachytherapy, respectively, the analysis included 880 molecularly classified cases; a total of 880 women with stage I EEC who had been allocated to EBRT, brachytherapy, or no adjuvant therapy [22,23] **(Figure 7)**.

The results showed that patients with POLE-mutated endometrial carcinoma had no locoregional recurrences, suggesting that even though POLEmut is the rarest molecular class of EC, the evidence for excellent outcomes regardless of adjuvant therapy is accumulating [24,25,26]. Therefore, radiotherapy could be safely omitted in this subgroup of patients. Mismatch repair-deficient endometrial carcinoma showed similar locoregional control across all treatment groups, indicating limited benefit from radiotherapy. However, for p53-abnormal endometrial carcinoma, radiotherapy significantly improved locoregional recurrence-free survival compared to vaginal brachytherapy or no therapy, making radiotherapy the preferred option for these molecularly-defined tumours. For endometrial carcinoma non-specific molecular profile, both radiotherapy and brachytherapy provided better locoregional control than no adjuvant therapy, with brachytherapy being as effective as radiotherapy [20].

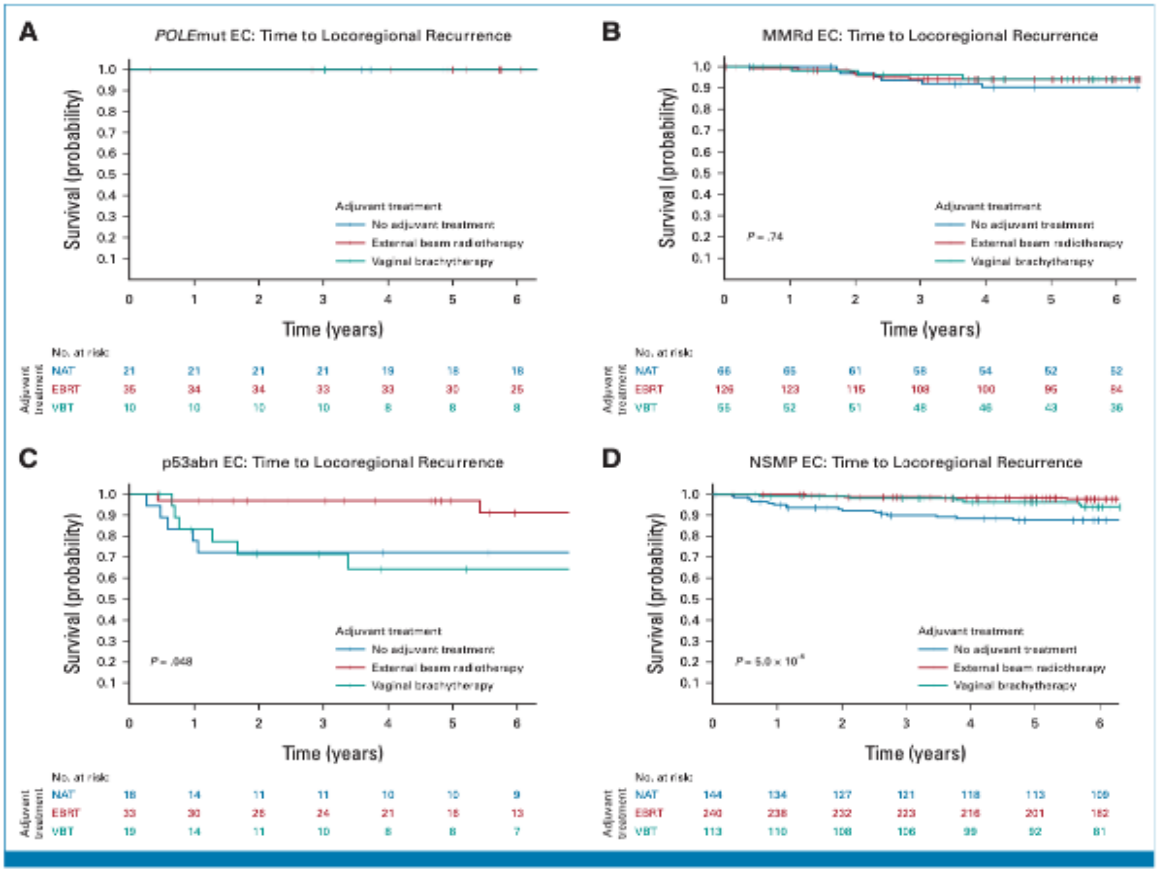


Figure 7: Time to locoregional recurrence per molecular class in PORTEC-1 and PORTEC-2.

(A) Time to locoregional recurrence in POLE-mutated endometrial cancer. (B) Time to locoregional recurrence in mismatch-repair deficient endometrial cancer. (C) Time to locoregional recurrence in p53 abnormal endometrial cancer. (D) Time to locoregional recurrence in no specific molecular profile endometrial cancer. EBRT, external beam radiotherapy; EC, endometrial cancer; MMRd EC, EC with mismatch repair deficiency (POLE wild-type); NAT, no adjuvant therapy; NSMP EC, EC with no specific molecular profile (POLE wild-type, MMR-proficient, and p53 wild-type); POLEmut EC, EC with a pathogenic mutation of DNA polymerase-e; p53abn EC, EC with a p53 abnormality (POLE wild-type and MMR-proficient); VBT, vaginal brachytherapy.

These findings suggest that molecular classification can guide adjuvant treatment decisions in early-stage endometrial carcinoma, tailoring radiotherapy based on specific molecular subtypes. Recent analyses of the PORTEC-3 trial confirmed the strong prognostic value of molecular classification in patients with high-risk tumour as per classical histological definition. Indeed, a significant benefit of chemoradiotherapy was found for p53abn, regardless of histologic type, while patients with POLE mutated had an excellent relapse-free survival in both arms [27].

Despite the growing body of evidence supporting the usefulness of molecular classification in tailoring adjuvant treatments to individual patients, it is important to recognize that access to this technology remains limited in many parts of the world, posing significant challenges to its widespread implementation.

3. Optimal sequencing of treatments

In exploring the optimal sequencing of treatments for advanced endometrial carcinoma, the randomized phase III LUNCHBOX trial evaluated the effectiveness of two different treatment sequences for advanced endometrial carcinoma: chemoradiotherapy followed by additional chemotherapy or a "sandwich" therapy, which involved chemotherapy both before and after radiation. The main objective was to determine whether the chemoradiotherapy then chemotherapy approach would lead to better recurrence-free survival compared to the sandwich method; to deliver a well-founded, evidence-based response regarding the optimal sequencing strategy for combined modality treatment in the management of advanced endometrial carcinoma, ensuring that the approach aligns with the most effective and clinically validated practices available. Due to low patient enrolment, the trial was stopped early after inclusion of 48 patients and the results were based on a median follow-up of 30.9 months. The findings showed no significant difference in 3-year relapse-free survival between the two groups, with the chemoradiotherapy followed by chemotherapy group at 85.7 % and the sandwich therapy group at 73.4 %. Similarly, overall survival rates were 88.4 % and 80.9 %, respectively. Adverse events were also similar between groups. The study concluded that there was no clear advantage of one treatment sequence over the other in terms of recurrence-free survival, overall survival, adverse events, or pattern of recurrence. While the trial permitted a prospective and clinically meaningful comparison of widely adopted standard-of-care combined modality treatment options for advanced endometrial cancer across

multiple institutions, the early closure of the trial because of slow accrual meant it was underpowered to detect smaller differences **(Figure 8)** [28].

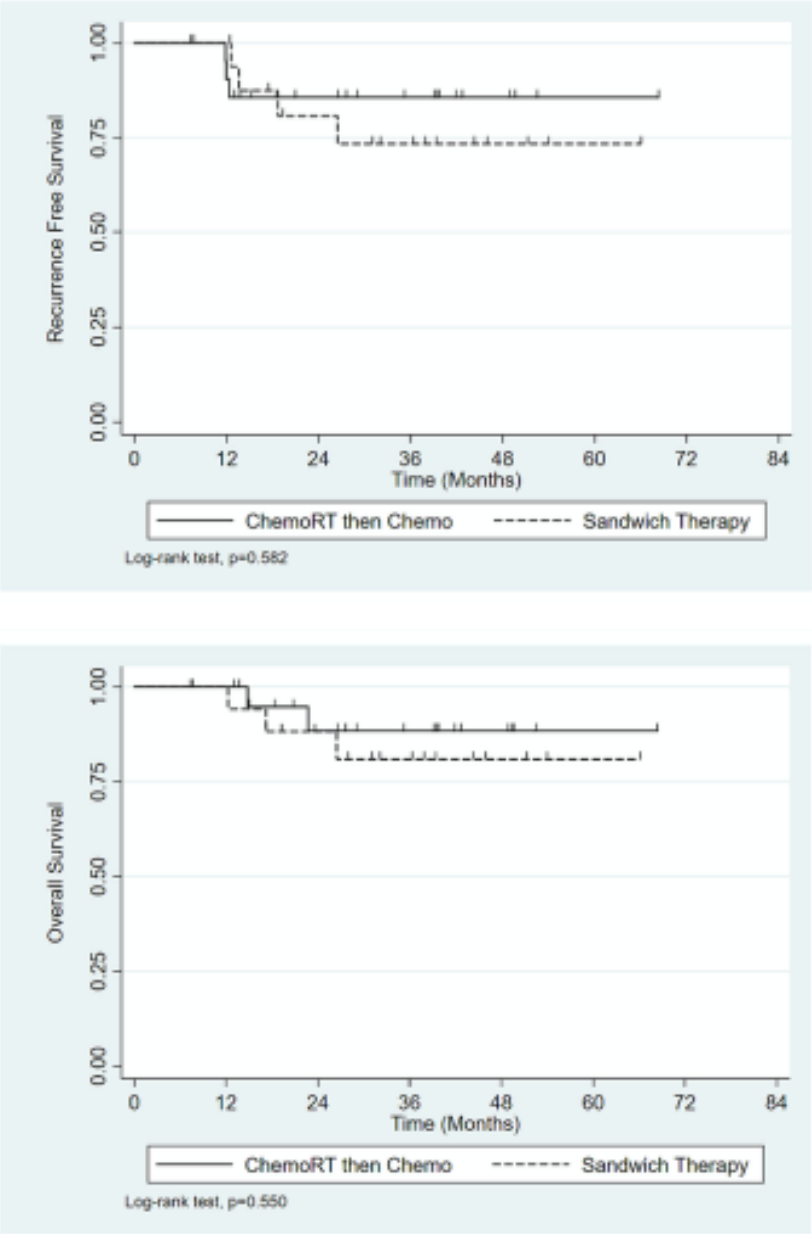


Figure 8: Kaplan-Meier survival curves of recurrence-free survival and overall survival for chemoradiotherapy followed by additional chemotherapy or a "sandwich" therapy in patients with advanced endometrial carcinoma (LUNCHBOX trial)

For now, the optimal sequence to combine adjuvant chemotherapy and pelvic radiotherapy, either as concurrent according to PORTEC-3 trial or as sequential, remains uncertain. In 2019, the randomized phase III Gynecologic Oncologic Group (GOG)-258 trial had reported results of 6-months of platinum-based chemotherapy plus radiotherapy versus only six cycles of chemotherapy for stage III or IVA endometrial cancers. 736 patients were included in the analysis, and the study did not show any difference in overall survival between both arms. More frequent distant failures were shown in the chemoradiotherapy arm, while more frequent locoregional relapses were seen in the chemotherapy only arm [29]. These findings align with the hypothesis proposed in prior research, suggesting that the successful completion of chemotherapy plays a critical role in reducing the risk of distant relapse in patients diagnosed with stage III or IVA endometrial carcinoma. In the continued effort to define the role of radiotherapy in the treatment of stage III endometrial cancer, a systematic review and meta-analysis published in 2023 explored the outcomes of patients with stage III endometrial cancer who underwent radical surgery followed by either adjuvant chemotherapy or adjuvant chemoradiotherapy. By analysing data from 16 studies involving 18,375 patients, the researchers found that those who received chemoradiotherapy had a significantly lower risk of both local and overall cancer recurrence compared to those who only received chemotherapy. Additionally, adjuvant chemoradiotherapy was linked to better overall, progression-free, and disease-free survival. These results suggest that adding radiotherapy to chemotherapy after surgery could be more effective in

reducing recurrence and improving survival rates, particularly for patients with stage IIIC endometrial cancer [30].

4. *Immunotherapy*

The role of immunotherapy as part of adjuvant treatments was explored in the ENGOT-en/GOG-3053/Keynote-B21 study, which assessed pembrolizumab versus placebo in combination with adjuvant chemotherapy, with or without radiotherapy, in patients with high-risk endometrial cancer. High-risk disease was defined as FIGO stage I/II with non-endometrioid histology or endometrioid histology accompanied by a TP53 mutation, or stage III/IVA of any histology. Unfortunately, the study was negative as it did not demonstrate an improvement in disease-free survival (DFS) with the addition of pembrolizumab to the standard chemotherapy regimen. However, a pre-planned subgroup analysis suggested a potential disease-free survival (DFS) benefit for patients with mismatch repair-deficient (MMRd) tumors [31], indicating a subgroup that might benefit from immunotherapy.

In contrast, the RUBY trial (ENGOT-EN6-NSGO/GOG3031) provided pivotal insights into the integration of immune checkpoint inhibitors with chemotherapy. This study evaluated the efficacy of dostarlimab, a PD-1 inhibitor, versus placebo, administered alongside carboplatin and paclitaxel in patients with primary advanced stage III or IV, or first recurrent endometrial cancer. Importantly, 24% of the enrolled patients had microsatellite instability-high (MSI-high) tumors, a biomarker often associated with better responsiveness to immune checkpoint inhibitors. The primary end points were progression-free survival and overall survival. The results were compelling,

showing a significant progression-free survival (PFS) benefit at 24 months with the inclusion of dostarlimab, particularly within the MSI-High population for whom a highly relevant clinical impact was shown (2-year progression free survival rates; 61.4% for the dostarlimab arm compared to 15.7% for the placebo arm (HR: 0.28, 95% CI: 0.16-0.50), demonstrating a remarkable clinical impact. However, the progression-free survival benefit was less evident in patients with stage III tumors, likely due to the small number of patients in this specific subgroup **(Figure 9)** [32].

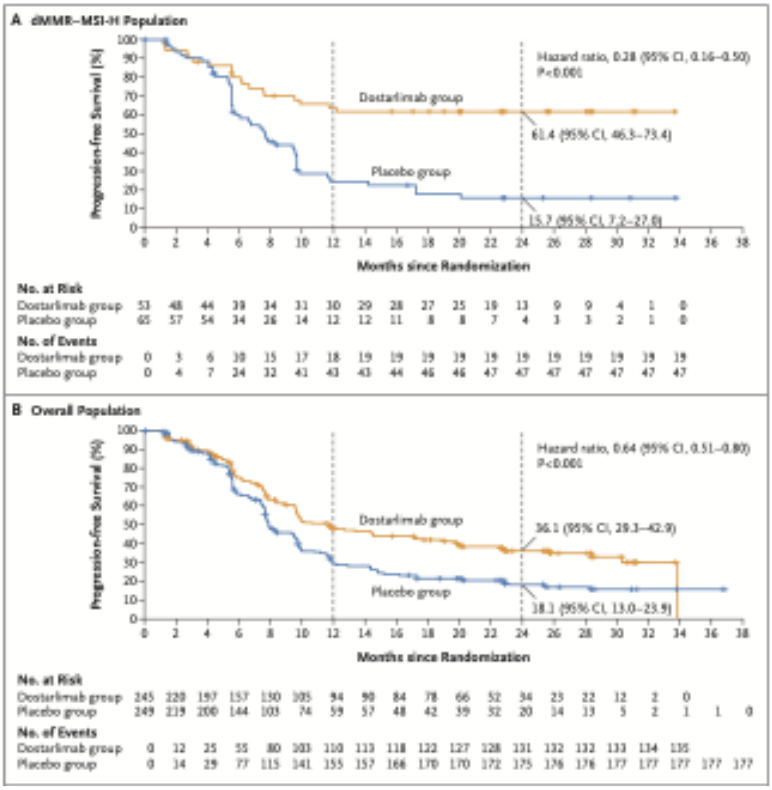


Figure 9: Kaplan-Meier estimates of progression free survival in the population with mismatch-repair-deficiency (dMMR), microsatellite instability-high (MSI-H) disease (panel A) and the overall population (panel B)

Dostarlimab plus carboplatin-paclitaxel significantly increased progression-free survival among patients with primary advanced or recurrent endometrial cancer, with a substantial benefit in the dMMR-MSI-H population, with the safety profile of the combined treatment being largely in line with the established safety profiles of each individual drug in the regimen. This finding highlights the heterogeneity of endometrial cancer and underscores the need for stratified treatment approaches based on tumor characteristics and staging. The contrasting outcomes of the Keynote-B21 and RUBY trials underscore the critical importance of carefully selecting patients to achieve the most effective outcomes with immunotherapy. These findings highlight the necessity of tailoring treatment strategies based on specific patient characteristics, including the biological and clinical profiles of their disease. This is particularly relevant in cases involving high-risk or advanced stages of cancer, where precise identification of eligible candidates for immunotherapy is crucial to maximizing therapeutic benefits. By considering factors such as tumor heterogeneity and individual risk profiles, these trials illustrate how thoughtful patient selection can significantly influence the success of innovative cancer treatments.

V. Unmet needs: Recurrent and rare tumours

1. *Place of radiotherapy for recurrent gynaecological tumours*

In evaluating the optimal approach for treating recurrent endometrial cancer, an NRG Oncology/GOG prospective randomized trial published in 2024 investigated whether the combination of chemotherapy with radiation therapy offers any significant advantage over radiation therapy alone, particularly focusing on progression-free survival (PFS) and the management of treatment-related toxicity [33]. The study enrolled 165 patients between 2008 and 2020, with most participants having low-grade endometrioid tumors and recurrences localized to the vagina. These patients were randomly assigned to receive either radiotherapy alone or radiotherapy in combination with weekly cisplatin-based chemotherapy.

The results revealed that patients treated with radiation therapy alone had a longer median progression free survival compared to those receiving chemoradiotherapy, with the median progression free survival not being reached in the radiation only group versus 73 months in the chemoradiotherapy group. Aditionally, the study demonstrated that the addition of chemotherapy was associated with higher rates of acute toxicity, including gastrointestinal and hematological side effects, highlighting that chemotherapy may introduce unnecessary risks without providing a significant survival benefit. After three years, 73% of the patients in the radiation-only group were alive and free from disease progression, compared to 62% in the chemoradiotherapy group **(Figure 10)**.

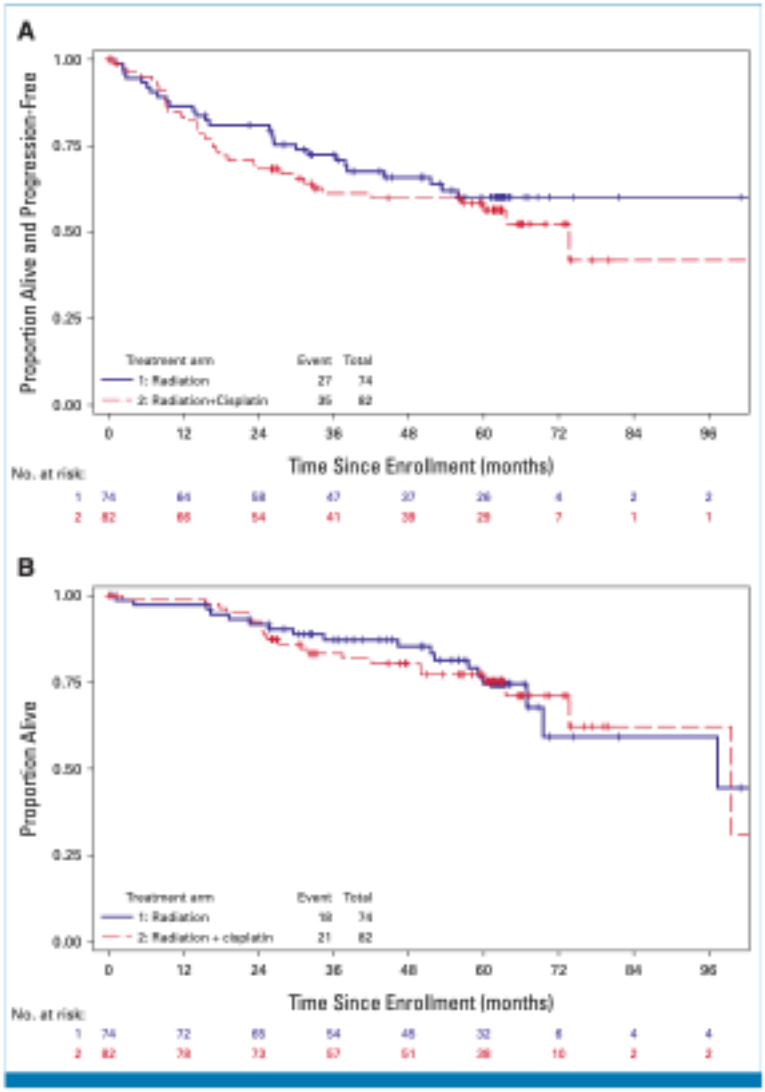


Figure 10: Kaplan-Meier curve comparing (A) PFS and (B) OS for patients treated with CRT versus RT alone in recurrent endometrial cancer.

These findings suggest that radiation therapy alone is highly effective for managing localized recurrences of endometrial cancer in patients with low-grade and vaginal recurrences. The addition of chemotherapy did not appear to confer additional benefit in terms of progression free survival but increased the frequency of acute toxic side effects, such as grade 3-4 nausea and cytopenia. However, it is important to emphasize that these results may not

be applicable to patients with high-grade or aggressive histologies, particularly when the recurrence involves nodal disease.

Moreover, molecular profiling was not available in this trial, limiting the ability to identify subgroups of patients who may benefit from concurrent chemoradiotherapy. Evidence from the PORTEC-3 trial has demonstrated a benefit of concurrent chemotherapy in patients with primary endometrial cancer harboring adverse molecular profiles, such as p53-mutated tumors. Thus, in the context of recurrent disease, molecular testing could play a pivotal role in guiding treatment decisions.

The adverse prognosis associated with second locoregional relapses also raises the need for further assessment and a personalized approach that considers both patient and tumor characteristics, including molecular biomarkers and disease burden. Emerging evidence supports the use of modern brachytherapy techniques for salvage treatments. Image-guided adaptive brachytherapy and reirradiation protocols have expanded the therapeutic options for patients, often avoiding the need for extensive surgeries such as pelvic exenteration [34,35].

In summary, the results of the NRG Oncology/GOG trial underscore the efficacy of radiation therapy alone for patients with low-grade, localized recurrences but also emphasize the need for individualized treatment strategies for those with high-risk features. Future research is essential to better define the potential benefits of systemic therapy in scenarios that were not directly evaluated in this trial, particularly as molecular subtype analysis, such as for p53-mutated tumors, was not conducted. Given that p53

mutations are associated with a favorable response to chemotherapy in the adjuvant setting, it is plausible that tumors with this molecular alteration may similarly benefit from the addition of chemotherapy in the recurrent setting. This possibility highlights the need for further studies to investigate the role of systemic therapy combined with radiation in diverse clinical settings and to explore how specific molecular subtypes, like p53-mutated tumors, influence treatment outcomes. By addressing these gaps, future research could provide critical insights into the optimization of therapeutic strategies tailored to tumor biology.

The incorporation of molecular testing, immune-oncology agents, and advanced radiation delivery techniques could further optimize outcomes and reduce treatment-associated morbidity, highlighting a path forward for improving care in recurrent endometrial cancer.

2. Vulvovaginal cancers

Vulvar and vaginal cancers are rare malignancies, representing only a small fraction of all gynaecologic cancers [36]. Surgery has a major role for vulvar cancer as upfront treatment. For vulvar cancer, radiotherapy is indicated as treatment of advanced cases, either prior to or adjuvant to surgery, or as exclusive treatment combined with chemotherapy when conservative surgical treatments cannot be achieved. For advanced cases, neoadjuvant chemoradiation followed with surgery achieves same outcomes as chemoradiation with or without brachytherapy boost [37]. For vaginal cancers, radiotherapy is the main treatment, combined with an image-guided brachytherapy boost [38]. The role of surgery is more marginal for primary

vaginal cancers, where only selected cases can be treated with partial colpectomy, provided that function preservation can be achieved. In 2023, the European guidelines were published for primary staging and treatment of both primary vaginal cancer and vulvar cancer, with a focus on various radiotherapy aspects in terms of indications and modalities [37,39]. However, very few prospective studies are available to guide radiotherapy place and techniques in these rare tumours.

Recent studies investigated the benefits of integrating chemotherapy with radiation therapy in vulvar cancer, aiming at enhancing tumour radiosensitivity and increase response rates. The NRG Oncology/GOG Study 279 was a phase II, single-arm clinical study designed to evaluate the efficacy and safety of combining cisplatin and gemcitabine with intensity-modulated radiotherapy for patients with locally advanced vulvar squamous cell carcinoma not amenable to surgery [40]. The trial included 57 patients with biopsy-confirmed stage II or III squamous cell carcinoma of the vulva, not amenable to surgical resection. The treatment regimen included weekly administration of cisplatin (40 mg/m^2) and gemcitabine (50 mg/m^2) alongside radiotherapy prescribed at 64 Gy to the vulva, with 50 to 64 Gy delivered to the groins and lower pelvis. The study demonstrated that concurrent use of cisplatin and gemcitabine with modern radiotherapy technique led to a complete pathologic response in 73 % of patients, with a 12-month progression-free survival rate of 74 % and a 24-month overall survival rate of 70 %. The most frequent grade 3 or 4 adverse events were hematologic toxicity and radiation dermatitis **(Figure 11 & Table 3)**.

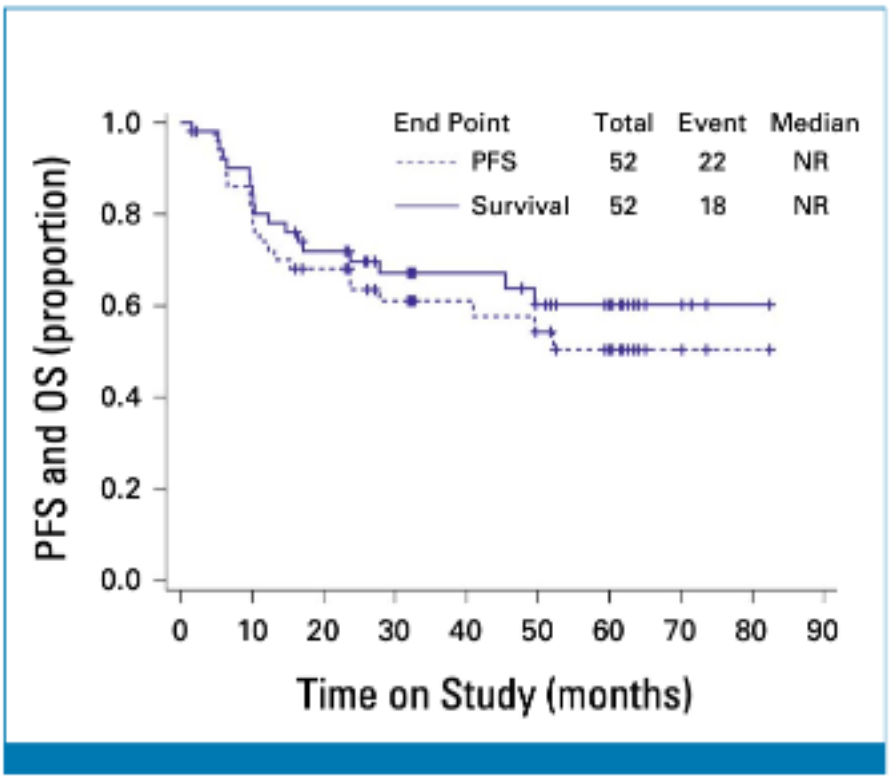


Figure 11: PFS at 12 months and OS at 24 months for Cisplatin and Gemcitabine combined with intensity-modulated radiotherapy in patients with locally advanced vulvar squamous cell carcinoma not amenable to surgery.

	Study		
Treatment/Outcome	GOG 101	GOG 205	Current/NRG 279
Radiation	4,760 cGy	5,670 cGy	6,400 cGy
Chemotherapy	Cisplatin + FU	Cisplatin	Cisplatin + Gem
Complete clinical response, %	48	64	71.2
Complete pathologic response, %	31	50	73.1
PFS at 12 months, %	NA	70	74

Table 3: Comparison of GOG/NRG Preoperative Chemoradiation Outcomes in Women with Locally Advanced Vulvar Cancer

Abbreviations: FU, fluorouracil; Gem, gemcitabine; GOG, Gynecologic Oncology Group, NRG Oncology; NA, not applicable; PFS, progression-free survival.

In conclusion, when compared with historical outcomes, the combination of gemcitabine and cisplatin administered weekly alongside intensity-modulated radiation therapy (IMRT) demonstrated a notable improvement in the complete pathological response (CPR) rate in women with locally advanced, unresectable squamous cell carcinoma (SCC) of the vulva. While the observed toxicities were generally tolerable, it remains uncertain whether this enhanced outcome can be attributed solely to the addition of gemcitabine or to the radiation intensification achieved through IMRT. These findings reinforce the effectiveness of treatment intensification with concurrent chemoradiotherapy with cisplatin and gemcitabine, though such protocol remains used only in experimental strategies, as evidence of superiority for this treatment approach over cisplatin only is lacking. Validation of these promising findings would necessitate the implementation of a randomized controlled trial. However, the design of such a trial would require careful consideration to ensure the inclusion of a diverse patient population, reflective of real-world clinical scenarios.

Moreover, it would be essential to account for the evolving landscape of therapeutic options, particularly the integration of emerging modalities such as immunotherapy, which may hold potential for further improving outcomes in this patient population. Throughout the course of the NRG Oncology/GOG Study 279, significant advancements were made in the development of

targeted therapies and immunotherapies, both as primary treatment options and as radiation sensitizers across various cancer types [41,42]. Specific molecular targets have been identified for squamous cell carcinomas (SCCs) of the vulva, offering potential therapeutic opportunities tailored to HPV-positive and HPV-negative subtypes [43]. For HPV-positive tumors, pathways such as phosphatidylinositol 3-kinase/mammalian target of rapamycin (PI3K/mTOR) have emerged as promising targets, while HPV-negative SCCs may benefit from interventions targeting P53, TERTp, CDKN2A, CCND1, and the epidermal growth factor receptor (EGFR).

One important research path for improving patient outcome is to better examine how recent molecular findings on the role of p53 mutations and PDL-1 expression may be implemented to refine prognostic stratification, predict response to treatment and identify requirements for dose escalation [40]. The KEYNOTE 258 trial demonstrated that durable responses can be achieved with pembrolizumab in women with recurrent vulvar SCC, irrespective of their PD-L1 expression status [44].Despite these promising developments, it remains uncertain whether incorporating immunotherapies or targeted agents into upfront chemoradiation regimens could further enhance complete pathological response (CPR) rates and overall survival outcomes beyond what was observed in this study. Future research is necessary to explore the potential synergy between these novel agents and standard chemoradiation approaches, particularly in the context of their molecular mechanisms and interactions with radiation. Such investigations could provide critical insights into optimizing treatment strategies for this challenging disease. Currently, a

single-arm phase II clinical trial is underway to evaluate the combination of pembrolizumab with cisplatin-sensitized radiation therapy in women diagnosed with unresectable, locally advanced, or metastatic vulvar cancer. This study aims to offer valuable insights into the efficacy of this treatment approach (ClinicalTrials.gov Identifier: NCT04430699).

VI. Conclusion

In the context of increased personalization of treatments, major studies recently challenged the historical standard of chemoradiotherapy for locally advanced cervical cancer. There remain uncertainties regarding which patients will benefit from these interventions that mainly rely on systemic intensification through induction chemotherapy or immunotherapy. Sustained dedication to research and clinical innovation will be essential in achieving further remarkable breakthroughs in the coming years, especially through integration of biomarkers to guide treatment efficacy and also by refining the role of dose escalation through modern image- guided brachytherapy in combination with this systemic approach. Among other investigational approaches, the randomized phase II PRO-PARA trial is investigating the impact of prophylactic para- aortic radiotherapy compared to pelvic only radiotherapy, phase III PAROLA trial is comparing para-aortic surgical staging and a risk-adapted strategy for prophylactic radiotherapy and randomized phase II ATEZOLACC trial is testing the place of atezolizumab in locally advanced cervical cancer. These studies will provide meaningful information on how to further improve patient outcome.

For endometrial cancer, recent developments in molecular and genetic profiling have ushered in a new era of tailored and precise therapies, shifting from a one-size-fits-all model to individualized treatment approaches. This precision medicine approach not only enhances treatment efficacy but also reduces adverse effects, thereby improving the overall quality of life for patients. Besides molecular advancements and recent developments to

integrate tumour biology better, there is an increasing emphasis on enhancing care quality through standardized treatment protocols and quality indicators. As shown in cervical cancer treatments, reducing variability in treatment approaches and improving patient out- comes on a broader scale remains crucial.

Finally, there remains a major need for developing research in rare tumours such as vulvar or vaginal cancers, where prospective trials remain necessary to guide further therapeutic strategies and improve patients outcome.

Table 1: Key Clinical Trials in Advanced Cervical Cancer Treatment

Trial	Objective	Design	Inclusion Criteria	Schema	Conclusion	Discussion
CALLA Trial [9]	Evaluate durvalumab + CRT vs placebo	Randomized, double-blind, placebo-controlled Phase III	FIGO IB2-IIB node+ or IIIA-IVA, PS 0-1, no prior treatment	Durvalumab + CRT, followed with durvalumab for 24 months vs. placebo + CRT, followed with placebo for 24 months	12-month PFS 76·0% with durvalumab vs 73·3% with placebo (not significant).	Need for further research in immunotherapeutic approaches (biomarkers)
KEYNOTE A-18 [10]	Evaluate pembrolizumab + CRT vs placebo	Randomized, double-blind, placebo-controlled Phase III	FIGO IB2-IIB node+ or IIIA-IVA, PS 0-1, no prior treatment	Pembrolizumab + CRT, followed with pembrolizumab x 15 cycles vs. placebo + CRT,	24-month PFS rates 68% in the pembrolizumab-CRT group versus 57% in the	Pembrolizumab was approved by FDA for stage III-IV (FIGO 2014).

				followed with placebo x 15 cycles	placebo-CRT group. Survival data update showed a benefit in OS	
OUTBACK Trial [11]	Evaluate adjuvant chemotherapy after CRT	Randomized controlled Phase III	IB1 with nodal involvement, IB2, II, IIIB, or IVA, suitable for primary treatment with CRT	Adjuvant chemotherapy (carboplatin and paclitaxel) vs. standard follow-up care	5-year OS was 72% in the adjuvant chemotherapy group and 71 in the CRT only group (difference 1% [95% CI -6 to 7] (not significant)	Highlighted the need for effective therapies to improve outcomes

INTERLACE Trial [12]	Evaluate induction chemotherapy followed by CRT	Randomized controlled, multi-center study	Squamous, adeno or adenosquamous carcinoma FIGO (2008) stage IB1 node positive, IB2, II, IIIB, IVA	CRT alone vs. induction chemotherapy (carboplatin and paclitaxel) followed by CRT	5-year PFS rate was 73% with induction versus 64% with upfront CRT (HR 0.65; 95%CI:0.46-0.91, p=0.013). The corresponding 5-year OS rates were 80% and 72% (HR 0.61:95%CI:0.40-0.91, p=0.04)	Publication awaited -preliminary data suggest a benefit of induction chemotherapy

FIGO: International Federation of Gynaecology and Obstetrics; HR: hazard ratio; 95 % CI: 95 % confidence interval; FDA: Food and Drug Administration, CRT: chemoradiation, OS: overall survival; PFS: progression-free survival; PS: performance status.

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