radiation

MDPI

Review

Beyond Photons: Emerging Advances and Clinical Potential of Proton Beam Therapy in Gynecological Malignancies

Lifeng Chen [1,2], Li Wang [1] and Hamid A. Bakshi [1,*]

[1] Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Rochester, MN 55905, USA; clf703@zju.edu.cn (L.C.); wang.li3@mayo.edu (L.W.)
[2] Department of Gynecology and Obstetrics, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China
* Correspondence: bakshi.hamid@mayo.edu

Simple Summary

This review article explains how proton beam therapy, a more precise form of radiation treatment, may improve care for women with gynecological cancers such as cervical, uterine, and ovarian cancer. Unlike traditional radiation, proton therapy can target tumors more accurately while reducing damage to nearby healthy organs like the bowel and bladder. This may help lower side effects and improve quality of life. The review also discusses current challenges, including high cost and limited availability, and highlights the need for more clinical studies in the future.

Abstract

Radiation therapy is central to the management of gynecological cancers, including endometrial, cervical, ovarian, and vaginal malignancies. Despite advances in photon-based techniques, treatment-related toxicity remains significant owing to the anatomical proximity of pelvic targets to critical organs at risk (OARs), including the bowel, bladder, and bone marrow. Proton beam therapy exploits the Bragg peak to deliver a precise dose at depth with minimal exit dose, potentially reducing OAR exposure. This review develops the physical principles, dosimetric evidence, and early clinical data for proton therapy in gynecological malignancies, including cervical, endometrial, ovarian, vaginal, and vulvar cancers. Major focus is given to clinical conditions where conventional brachytherapy is not practical, and proton therapy may offer the greatest advantages, such as reirradiation for recurrent disease, post-operative pelvic irradiation, and extended field nodal treatment. This review also emphasizes current constraints that have slowed down wide clinical implementation, such as the lack of mature prospective data, cost, and accessibility. Finally, we emphasize future directions, including well-designed comparative trials, integration with systemic and immunotherapies, and adaptive treatment strategies. As the body of accumulated evidence evolves, the proton beam therapy potential for the treatment of gynecological malignancies has tremendously increased due to its role in safety and personalization of radiation treatment.

Keywords: proton beam therapy; gynecological cancers; radiation oncology; cervical cancer; endometrial cancer; ovarian cancer; pelvic irradiation; dosimetry; organs at risk; reirradiation; adaptive radiation therapy; proton therapy; radiation toxicity; precision medicine; FLASH radiotherapy

Academic Editor: Jason Parsons

Received: 2 May 2026
Revised: 13 June 2026
Accepted: 23 June 2026
Published: 30 June 2026

1. Introduction

Gynecological malignancies, encompassing cancers of the cervix, endometrium, ovary, vagina, and vulva, represent a significant global health burden affecting women across all age groups. Radiation therapy plays a pivotal role in the curative and palliative management of these diseases, either as definitive treatment, adjuvant therapy following surgery, or in the reirradiation setting for recurrent disease [1]. Despite advances in photon-based radiation techniques, including intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT), treatment-related toxicities remain a substantial clinical challenge due to the anatomical proximity of gynecological targets to critical pelvic organs at risk (OARs) [2].

The pelvic anatomy presents unique challenges for radiation delivery [3]. The bladder, rectum, sigmoid colon, small bowel, and pelvic bone marrow are in close proximity to gynecological treatment volumes, making it difficult to achieve adequate target coverage while minimizing normal tissue exposure with conventional photon techniques [4]. Acute toxicities, including diarrhea, cystitis, proctitis, and hematologic suppression, can compromise treatment completion and quality of life during therapy. Late complications such as chronic enteritis, fistula formation, pelvic insufficiency fractures, and secondary malignancies can have profound long-term impacts on survivors [4].

Proton beam therapy represents a paradigm shift in radiation oncology, leveraging fundamental physical properties that distinguish protons from photons [5]. The finite range of protons in tissue and the characteristic Bragg peak, a sharp increase in energy deposition at the end of the proton's path, enable precise dose delivery with minimal exit dose beyond the target [6,7]. This physical advantage translates into the potential for superior sparing of normal tissues while maintaining or improving target coverage. For gynecological malignancies, where treatment volumes often encompass large pelvic fields and where patients may be young with long life expectancies, the promise of reduced integral dose and OAR exposure is particularly compelling [8,9].

The rationale for proton therapy in gynecological cancers is multifaceted [10]. First, dosimetric modeling consistently predicts substantial reductions in dose to critical structures, which may translate into decreased acute and late toxicity. Second, reduced bone marrow exposure may preserve hematologic function during concurrent chemotherapy, potentially allowing for better treatment compliance and dose intensity. Third, a lower integral body dose may reduce the risk of secondary malignancies, an important consideration for younger patients with favorable prognoses. Fourth, in the reirradiation setting, proton therapy's ability to minimize dose to previously irradiated tissues may expand treatment options for patients with recurrent disease.

However, it is important to note that the current evidence base consists predominantly of dosimetric planning studies and small retrospective or registry cohorts. No randomized controlled trial has yet demonstrated clinical superiority of proton over modern photon therapy in gynecological malignancies. Dosimetric advantages, while consistent and promising, must therefore be clearly distinguished from proven clinical benefit, and all claims of reduced toxicity or improved outcomes should be considered preliminary pending prospective validation [11].

This comprehensive review aims to synthesize the current state of knowledge regarding proton beam therapy for gynecological malignancies. We examine the physical and radiobiological principles underlying proton therapy, critically analyze dosimetric comparisons with photon techniques, review clinical outcomes by disease site, discuss special treatment scenarios, explore integration with systemic therapies and adaptive approaches, and identify current limitations and future research directions. Our goal is to provide radiation oncologists, gynecologic oncologists, and other stakeholders with an evidence-

based framework for understanding the role of proton therapy in the contemporary management of gynecological cancers.

A systematic search of PubMed/MEDLINE, EMBASE, and ClinicalTrials.gov was conducted using the MeSH terms and keywords: "proton therapy," "proton beam therapy," "gynecological malignancies," "cervical cancer," "endometrial cancer," "ovarian cancer," "vaginal cancer," "vulvar cancer," "radiation therapy," "dosimetry," "toxicity," and "NTCP." The search spanned publications from inception through March 2026 and was restricted to English-language articles. Studies were included if they reported original dosimetric comparisons, clinical outcomes, or review data pertaining to proton therapy in gynecological cancers. Case reports with fewer than three patients, non-English articles, and conference abstracts without full data were excluded. Two authors independently screened titles and abstracts, with discrepancies resolved by consensus.

2. Physical Principles and Radiobiological Basis of Proton Therapy

2.1. Fundamental Physics of Proton Beam Interactions

Proton beam therapy exploits fundamental differences in the physical interactions of charged particles compared to photons as they traverse tissue. Unlike photons, which deposit dose exponentially along their path with maximum dose near the surface and continuous exit dose beyond the target, protons exhibit a characteristic depth–dose distribution known as the Bragg peak [12,13].

Modern proton therapy employs pencil-beam scanning (PBS) technology, which delivers treatment using magnetically steered narrow proton beamlets of varying energies and intensities. This approach enables intensity-modulated proton therapy (IMPT), analogous to photon IMRT, where the three-dimensional dose distribution is optimized by modulating the number of protons delivered to each spot position and energy layer. IMPT provides superior dose conformality compared to passive scattering techniques and allows for sophisticated optimization strategies, including robust optimization to account for uncertainties [14,15]. This phenomenon arises from the inverse relationship between proton energy and linear energy transfer (LET): as protons slow in tissue, they deposit increasing amounts of energy per unit path length, culminating in a sharp peak at the end of their range, followed by a rapid dose fall-off [16].

The depth of the Bragg peak is determined by the initial proton energy, with higher energies penetrating deeper into tissue [Figure 1A,B].

Clinical proton therapy systems typically generate proton beams with energies ranging from 70 to 250 MeV, corresponding to ranges in tissue from approximately 4 to 38 cm. This finite range is a critical advantage, as it eliminates exit dose beyond the target volume, a fundamental limitation of photon therapy that cannot be overcome by any beam arrangement or optimization strategy [17].

https://doi.org/10.3390/radiation6030023

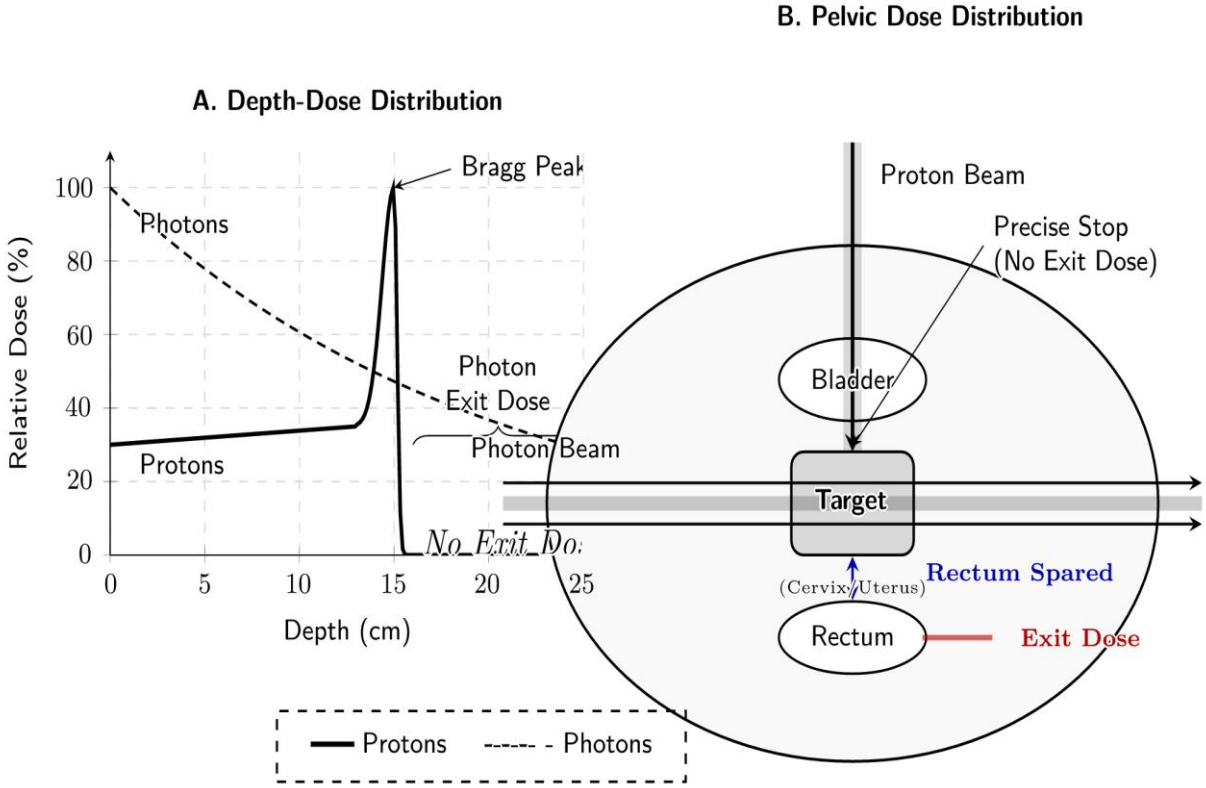

Figure 1. Comparison of depth–dose distributions between protons and photons. (**A**) The physical advantage of proton therapy is characterized by the Bragg peak. Conventional megavoltage photons (dashed line) demonstrate an initial dose build-up followed by exponential attenuation, resulting in a significant exit dose beyond the target volume. In contrast, the proton beam (solid line) maintains a low entry dose and deposits most of its energy at a specific, adjustable depth, with a rapid distal fall-off and no exit dose. This property allows for superior sparing of healthy tissues located deep to the tumor. (**B**) Cross-sectional representation of the clinical application of proton therapy in the pelvis. The proton beam (indicated by the directional arrow) achieves a precise stop within the target volume (cervix/uterus). Because the beam does not traverse the entire body like a standard photon beam, posterior organs at risk, such as the rectum, are spared from unnecessary radiation exposure, thereby reducing the "integral dose" to the patient. This visualization highlights the reduction in the "integral dose" to the patient. Created in BioRender. Bakshi H. (2026) https://BioRender.com/Basic.

2.2. Relative Biological Effectiveness

A critical consideration in proton therapy is the relative biological effectiveness (RBE), which quantifies the biological effect of proton radiation relative to photon radiation for a given absorbed dose [18]. Current clinical practice employs a generic RBE value of 1.1, meaning that 1 Gy of proton dose is considered biologically equivalent to 1.1 Gy of photon dose. This value is based on extensive in vitro and in vivo experimental data and has been used throughout the history of clinical proton therapy [18]. According to AAPM TG-256, RBE values at the distal edge of the SOBP can range from approximately 1.1 to 1.7 depending on dose per fraction, tissue alpha/beta ratio, and LET [19]. For posterior and lateral proton beam arrangements in pelvic treatments, the posterior bladder wall and anterior rectal wall may reside at or near the distal field edge, where RBE enhancement is greatest. Underestimation of biological dose in these OARs under a fixed RBE = 1.1 assumption represents a clinically meaningful uncertainty, particularly for hypofractionated schedules or high-LET beam arrangements. Research groups are developing variable-RBE treatment-planning models [20]; however, insufficient clinical evidence currently

supports departing from the fixed RBE = 1.1 for routine practice. Oncologists applying proton therapy to pelvic targets should nevertheless be aware of this biological uncertainty, particularly when OARs are deliberately positioned near distal field edges.

2.3. Dosimetric Advantages: Theoretical Framework

The physical properties of protons translate into several dosimetric advantages relevant to gynecological malignancies:

Reduced integral dose: The absence of exit dose and the concentrated energy deposition in the Bragg peak result in substantially lower integral dose to the patient compared to photon techniques [11]. This is particularly relevant for large pelvic treatment volumes where photon plans necessarily irradiate significant volumes of normal tissue [21]

Improved dose conformality**:** IMPT can achieve highly conformal dose distributions that closely match complex target geometries while respecting dose constraints to adjacent OARs. The ability to control dose deposition in three dimensions with minimal proximal and no distal dose provides degrees of freedom not available with photon therapy [22].

Reduced low-dose bath**:** Photon IMRT, particularly with multiple beam angles, creates a characteristic low-dose bath throughout the pelvis and abdomen [22]. Proton therapy dramatically reduces the volume of tissue receiving low doses (e.g., V5Gy, V10Gy), which may be relevant for reducing secondary malignancy risk and preserving bone marrow function [22].

Organ-specific sparing: For gynecological targets, proton therapy can selectively spare specific OARs based on their geometric relationship to the target [23]. Anteriorly located bladder, posteriorly located rectum and sigmoid, superiorly located small bowel, and circumferentially distributed pelvic bone marrow can all benefit from reduced dose exposure [23]. As illustrated in Figure 2, the unique physical properties of the proton beam allow for high-dose conformality to the endometrial target while ensuring a rapid distal fall-off that protects these critical adjacent structures.

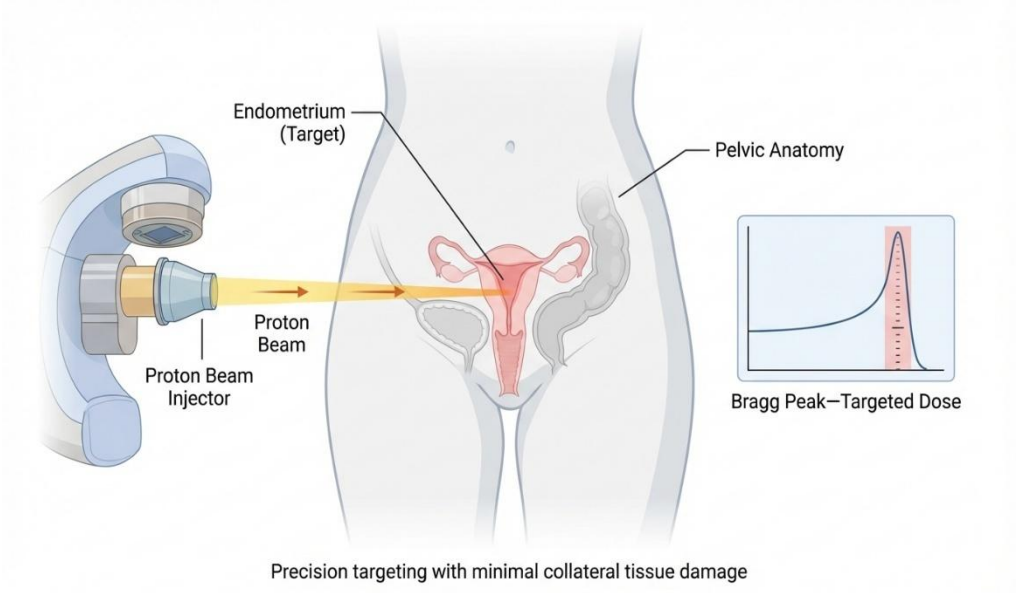

Figure 2. Schematic of targeted proton delivery in endometrial malignancy. This illustration demonstrates the clinical application of the Bragg peak for precision dose deposition within a gynecological target known as critical target volume (CTV). The proton injector delivers a modulated beam that conforms to the geometry of the tumor while ensuring a rapid distal fall-off. This mechanical property allows for the delivery of therapeutic doses to the primary site while effectively sparing critical adjacent organs at risk (OARs), specifically the anteriorly located bladder and the posteriorly located

rectum and sigmoid colon, thereby minimizing the integral dose to healthy pelvic tissue. Created in BioRender. Bakshi H. (2026) https://BioRender.com/Basic.

These theoretical advantages provide the foundation for clinical investigation of proton therapy in gynecological malignancies, with the goal of translating dosimetric improvements into clinically meaningful reductions in toxicity and improvements in quality of life.

3. Dosimetric Comparisons with Photon-Based Techniques

3.1. Methodology of Comparative Planning Studies

It must be emphasized that no randomized controlled trial has yet demonstrated clinical superiority of IMPT over modern photon techniques in gynecological malignancies. The dosimetric evidence reviewed here is, by definition, hypothesis-generating. Statements regarding predicted toxicity reductions should be framed accordingly throughout the manuscript [24].

Proton Therapy Versus Modern Adaptive Photon Techniques

A clinically pivotal question is whether IMPT provides meaningful dosimetric or clinical benefit beyond state-of-the-art adaptive photon approaches, including MR-guided radiotherapy (MRgRT) and online adaptive IMRT/VMAT. Available dosimetric comparisons indicate that modern adaptive photon platforms substantially reduce OAR dose versus conventional IMRT; however, IMPT continues to show incremental advantages in low-dose bath reduction (V5Gy, V10Gy) to small bowel and pelvic bone marrow—metrics less amenable to improvement through beam-angle optimization alone. The dosimetric margin between modern adaptive photon and proton approaches is nonetheless narrowing. No prospective clinical trial has demonstrated that IMPT is superior to state-of-the-art adaptive photon therapy in terms of patient-reported or clinician-graded outcomes in gynecological malignancies [25].

3.2. Small-Bowel Dose Reduction

Small-bowel toxicity represents one of the most significant dose-limiting factors in pelvic radiation therapy [26]. Acute enteritis, manifesting as diarrhea, cramping, and malabsorption, can compromise treatment completion and quality of life, while late complications, including stricture, obstruction, and fistula formation, can be devastating. Multiple dosimetric studies have demonstrated substantial small-bowel sparing with IMPT compared to photon techniques [26].

In a landmark intra-individual comparison by Marnitz et al. involving 20 patients with locally advanced cervical cancer, IMPT reduced mean small-bowel dose by 38–52% compared to photon techniques (IMRT, helical tomotherapy, and VMAT) [23]. For patients receiving pelvic irradiation, the mean small-bowel dose decreased from 30.2 to 34.1 Gy with photon techniques to 18.6 Gy with IMPT. For extended-field radiation therapy (EFRT) including para-aortic nodes, the reduction was even more pronounced, from 24.0 to 26.3 Gy to 13.8 Gy. Importantly, the volume of small bowel receiving low doses (V10Gy) was reduced by approximately 50% with IMPT, which may be particularly relevant for reducing acute toxicity [23].

Boer et al. investigated the combination of MRI-based target tailoring and IMPT for cervical cancer, demonstrating that IMPT alone reduced the NTCP for Grade ≥2 acute small-bowel toxicity from 25% to 18%, with further reduction to 9% when combined with adaptive target tailoring [27]. This study highlighted that IMPT provides clinically meaningful reductions in predicted toxicity, with NTCP reductions exceeding 10% when baseline small-bowel V45Gy exceeded 275 cm^3 [27].

Hashimoto et al. compared spot-scanning proton therapy (SSPT) with IMRT and 3D-CRT for whole-pelvic radiotherapy in 10 cervical cancer patients, finding that SSPT resulted in lower median V20 values for the small intestine and superior mean dose sparing compared to other modalities [28]. The homogeneity and conformity indices were also favorable for SSPT, suggesting improved dose distributions [28].

3.3. Bladder and Rectum Sparing

Bladder and rectal toxicities, including cystitis, proctitis, bleeding, fistula formation, and functional impairment, significantly impact quality of life for gynecological cancer survivors. Dosimetric studies have consistently shown reductions in bladder and rectum dose with IMPT, though the magnitude of benefit varies depending on target location and field arrangement.

Marnitz et al. reported that IMPT decreased the mean dose to bladder and rectum by approximately 7–9 Gy compared to photon approaches in the same patients [23]. While these reductions are less dramatic than those observed for the small bowel, they may still translate into clinically meaningful toxicity reductions, particularly for late effects where dose–response relationships are steep.

Shang et al. performed a detailed robustness analysis comparing IMPT with helical IMRT for cervical cancer, demonstrating that robustly optimized IMPT achieved lower NTCP values for rectum (2.8% vs. 4.8%, $p < 0.05$) and sigmoid colon (5.2% vs. 5.7%, $p < 0.05$) compared to IMRT [29]. This study employed sophisticated robust optimization techniques to account for setup and range uncertainties, providing more clinically realistic estimates of achievable dose distributions [29].

For boost treatments in cervical cancer, Sharma et al. compared pencil-beam scanning with photon-based stereotactic body radiation therapy (SBRT) in patients unable to receive brachytherapy, finding that PBS significantly reduced integral dose to normal tissues and achieved lower maximum doses to bladder and rectum [30]. However, it is important to note that even advanced external beam techniques, including IMPT, generally remain inferior to high-quality image-guided brachytherapy for cervical cancer boost treatments, as demonstrated by Georg et al. [4].

3.4. Pelvic Bone Marrow Sparing

Preservation of pelvic bone marrow (PBM) function is particularly important in gynecological malignancies, where concurrent chemotherapy is standard for many patients. Hematologic toxicity can lead to treatment delays, dose reductions, or discontinuation of chemotherapy, potentially compromising oncologic outcomes. Additionally, bone marrow suppression may impair immune function, which is increasingly recognized as relevant for both tumor control and response to immunotherapy.

Multiple studies have demonstrated substantial PBM sparing with proton therapy. Wark et al. conducted a matched-pair cohort study of 50 patients (25 IMPT, 25 IMRT) with cervical or endometrial cancer receiving postoperative radiation, finding that IMPT significantly reduced integral dose to the pelvic skeleton (23.4 Gy[RBE] vs. 34.3 Gy, $p < 0.001$) [31]. Average V5Gy, V10Gy, and V20Gy to the pelvic skeleton were reduced by 40%, 41%, and 28%, respectively ($p < 0.001$). This dosimetric advantage translated into significantly less hematotoxicity in the IMPT group (32% vs. 80%, $p = 0.0009$), with particularly striking reductions in Grade ≥2 hematotoxicity (8% vs. 36%, $p = 0.037$) [31]. This correlation between reduced skeletal dose and improved clinical hematologic outcomes is visually summarized in Figure 3.

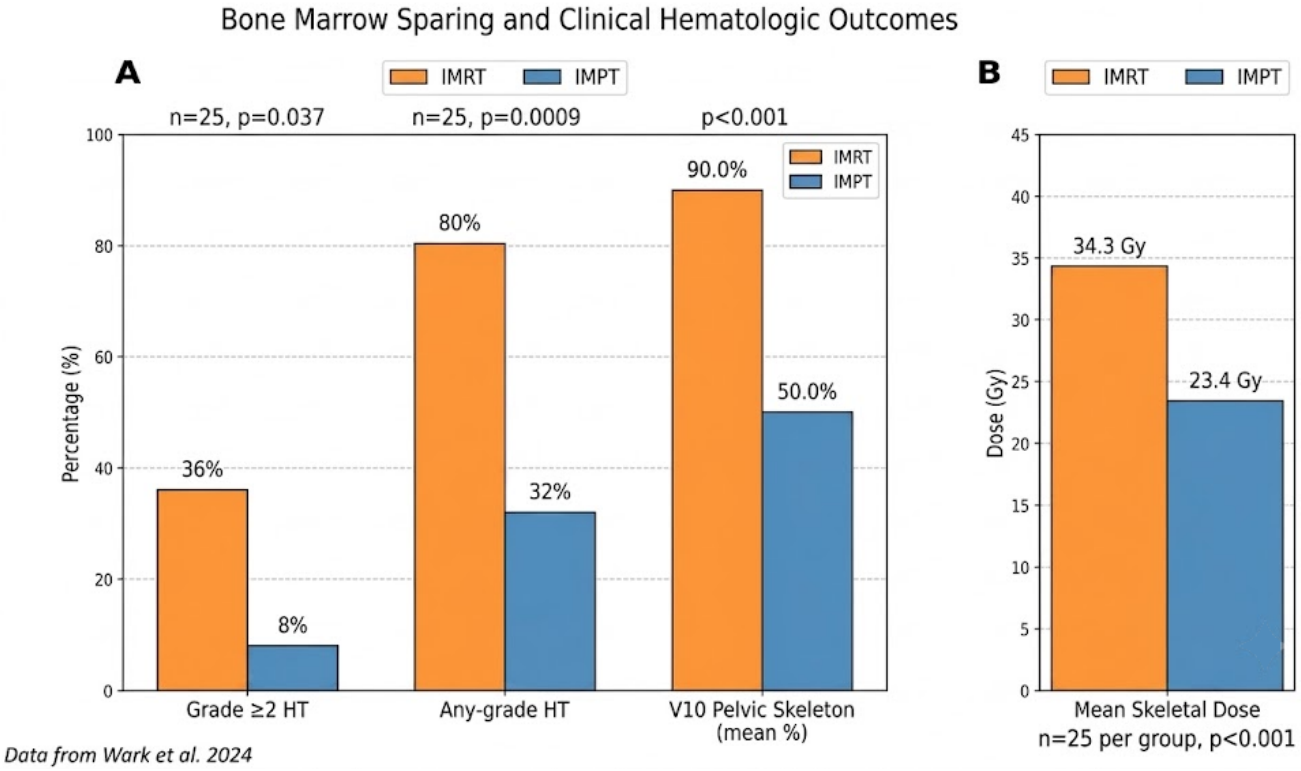

Figure 3. Impact of IMPT on bone marrow sparing and hematologic outcomes. Data from [32] (IMPT n = 25, IMRT n = 25, matched-pair cohort). (**A**) Grade ≥2 HT: 8% (IMPT) vs. 36% (IMRT), p = 0.037. Any-grade HT: 32% (IMPT) vs. 80% (IMRT), p = 0.0009. V10 pelvic skeleton shown as a mean percentage. (**B**) Mean skeletal dose: 23.4 Gy (IMPT) vs. 34.3 Gy (IMRT), $p < 0.001$. Sample sizes (n = 25 per group).

Xu et al. evaluated extended-field radiation for endometrial cancer, comparing pencil-beam scanning (PBS) with IMRT in 25 patients [25,32]. PBS resulted in 22% lower median PBM volume irradiated to 10 Gy[RBE] (71.3% vs. 93.4%, $p < 0.001$), with significantly lower dose volumes across the range from 0 to 26 Gy [25,32]. This is particularly relevant for extended-field treatments, where large volumes of bone marrow are at risk.

Song et al. compared IMRT with three-dimensional conformal proton therapy (3DCPT) specifically for PBM sparing in cervical cancer, demonstrating that 3DCPT showed superiority in reducing lower doses (V30 or less) to PBM, with average V10 and V20 reductions of 10.8% (p = 0.001) and 7.4% (p = 0.04), respectively [33]. Interestingly, IMRT provided better sparing for higher doses (>V30), highlighting the complementary strengths of different techniques [33].

Lin et al. reported that PBS significantly lowered the volume of pelvic bone marrow receiving 10 to 30 Gy compared to IMRT ($p < 0.05$) in 11 posthysterectomy patients, while maintaining target coverage robustness [34]. This early clinical feasibility study provided proof-of-concept that the dosimetric advantages observed in planning studies could be realized in clinical practice [34]. The integrated clinical and dosimetric advantages of proton beam therapy (PBT) synthesized from these representative studies are summarized in Table 1. By consolidating the quantitative sparing of the gastrointestinal, hematological, and genitourinary systems, this summary underscores the superior therapeutic ratio of IMPT over traditional photon-based modalities. It further highlights the mechanical necessity of advanced delivery techniques, such as pencil-beam scanning and adaptive replanning, to maintain these clinical gains.

Several confounding factors should be considered when interpreting reported hematologic toxicity differences between proton and photon cohorts. First, bone marrow con-

touring methodology varies widely: some studies contour the whole pelvic skeleton while others use MRI-derived active marrow subvolumes, producing non-comparable dose–volume metrics. Second, radiation field extent (pelvis-only vs. extended-field para-aortic) substantially affects the bone marrow volume irradiated, confounding cross-study comparisons. Third, chemotherapy regimen details—cisplatin dose intensity, weekly versus triweekly scheduling, and concurrent bevacizumab—independently modulate hematologic toxicity and were not uniformly reported. Fourth, patient-level factors, including baseline blood counts, prior chemotherapy exposure, and body habitus, represent additional confounders rarely controlled in available studies. Future investigations should adopt standardized bone marrow contouring protocols and report full chemotherapy regimen details to enable valid comparisons.

Table 1. Summary of dosimetric sparing and clinical outcomes in pelvic PBT.

Clinical Domain	Dosimetric Metric (PBT vs. IMRT/VMAT)	Clinical Significance	Patient *n*	Key Reference(s)	Associated Figure
Gastrointestinal (GI)	38–52% reduction in mean small-bowel dose (V15Gy–V45Gy)	Significant decrease in acute Grade 2+ diarrhea and enteritis	*n* = 20 (pelvic); *n* = 10 (EFRT)	Marnitz et al. [23] Boer et al. [27] Hashimoto et al. [28]	Figures 2 and 3
Hematological (BM)	Lower V10Gy/V20Gy to the pelvic bone marrow skeleton; mean skeletal dose reduced from 34.3 Gy (IMRT) to 23.4 Gy (IMPT)	Reduction in Grade 2+ neutropenia (from 36% to 8%) during cisplatin-based chemoradiation	*n* = 50 (25 IMPT, 25 IMRT); *n* = 25 (EFRT)	Wark et al. [31] Xu et al. [25] Song et al. [33] Lin et al. [34]	Figures 3 and 5
Genitourinary (GU)	Mean bladder dose reduction of 7–9 Gy	Potential for improved long-term urinary function and reduced urgency	*n* = 20	Marnitz et al. [23]	Figures 3 and 6
Target Coverage	Superior conformality using pencil-beam scanning (PBS); DVH band widths 0.6% vs. 2.1% (IMPT vs. IMRT)	Maintenance of target coverage (V95%) despite proximity to OARs under robust optimization	*n* = 18 (robustness); *n* = 11 (postop. PBS)	Shang et al. [29] Lin et al. [34]	Figure 1
Technical Delivery	Necessity of adaptive replanning protocols; CTV centroid shift >3 mm triggers plan adaptation	Mitigates range uncertainties caused by bladder and rectal volume shifts during treatment	Multiple studies	Shang et al. [29] Yoshimura et al. [3] PROTECT trial [35]	Figures 4 and 7

3.5. Normal Tissue Complication Probability Modeling

Beyond simple dose-volume metrics, several studies have employed NTCP modeling to estimate the clinical impact of dosimetric differences. Yoshimura et al. (*n* = 13) compared ro-IMPT, 3D-CRT, and IMXT, finding median NTCP for acute hematologic toxicity of 0.06 (ro-IMPT) versus 0.20 (3D-CRT) and 0.19 (IMXT); for late gastrointestinal toxicity, 0.15×10^{-1} versus 0.58×10^{-1} and 0.24×10^{-1}, respectively [3,33]. These modeling results suggest clinically meaningful predicted toxicity reductions.

A critical methodological caveat is that established NTCP models—including the Lyman–Kutcher–Burman and logistic regression models—were derived from photon

dose–volume datasets. The spatially distinct dose distributions produced by proton therapy, particularly the steeper dose gradients and markedly reduced low-dose bath, may not conform to photon-derived dose–response relationships. Furthermore, variable RBE introduces additional biological uncertainty at tissue interfaces in the distal fall-off region, potentially causing NTCP models to under- or over-estimate actual complication probabilities. It is therefore an important research priority to develop proton-specific NTCP models derived from prospective proton cohorts with standardized dose reporting, rather than relying solely on photon-derived surrogates [34].

3.6. Target Coverage and Plan Robustness

A critical consideration in proton therapy is plan robustness—the ability of the plan to maintain adequate target coverage and OAR sparing in the presence of uncertainties, including setup errors, organ motion, and proton range uncertainties. Unlike photon therapy, where dose distributions are relatively insensitive to small positional changes, proton therapy is vulnerable to range uncertainties arising from CT Hounsfield unit conversion errors, tissue heterogeneities, and anatomical changes [28]. This dynamic interaction between anatomical shift and range uncertainty is detailed in the adaptive re-planning cycle shown in Figure 4.

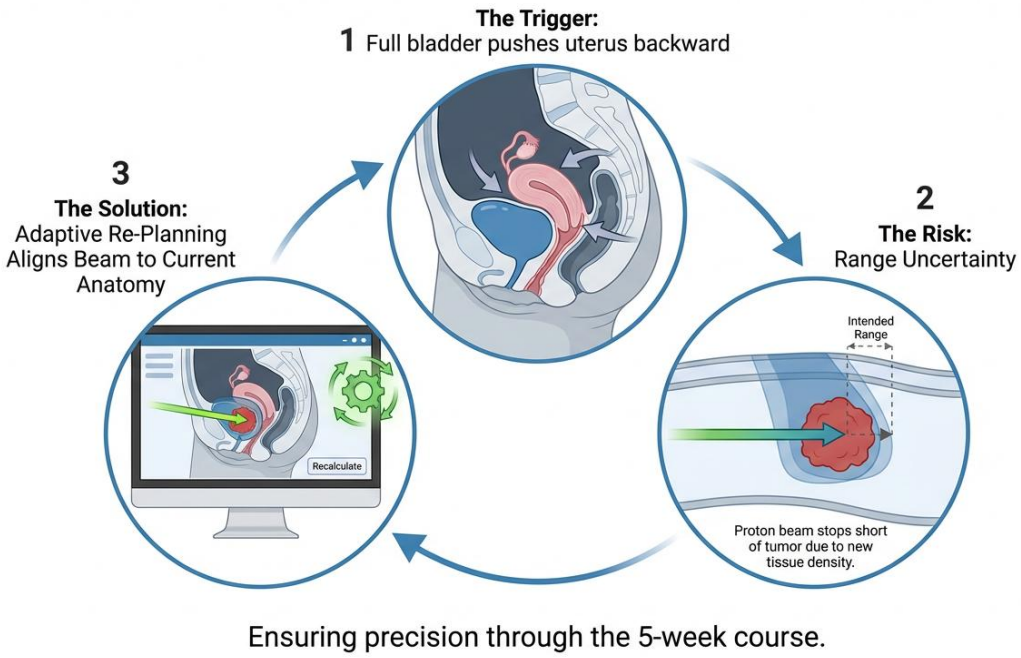

Figure 4. The adaptive re-planning cycle: ensuring precision amidst anatomical variation. This schematic illustrates the clinical workflow required to manage the unique physical properties of proton beams during a 5-week pelvic radiation course. 1. The Trigger (Anatomical Shift): Physiological changes, such as a full bladder, can push the target volume (uterus) backward, deviating from the original static treatment plan. 2. The Risk (Range Uncertainty): Because protons stop at a specific depth based on tissue density, this shift causes the beam to stop short of the intended target, potentially under-dosing the tumor. 3. The Solution (Adaptive Re-Planning): Routine verification imaging triggers a recalculation of the plan, aligning the beam to the current anatomy to ensure robust target coverage and optimal sparing of surrounding organs at risk. Created in BioRender. Bakshi H. (2026) https://BioRender.com/basic.

Practical Motion Management and Adaptive Replanning Workflows

Interfractional anatomical variation is a fundamental challenge in pelvic proton therapy. Bladder and rectal filling fluctuations directly alter tissue density along beam paths

and shift the Bragg peak position. Standard clinical mitigation strategies include (1) preparation protocols: standardized voiding instructions, timed oral hydration for consistent bladder filling, and endorectal balloons in selected patients to reduce rectal volume variability; (2) plan libraries: generation of 2–3 contingency plans from planning CTs obtained at different bladder-filling states, with daily selection of the best-matching plan based on online imaging (offline adaptive approach); (3) adaptive replanning triggers: most centers initiate offline or online replanning when daily imaging demonstrates CTV centroid shift >3 mm, D95 target coverage fall >5%, or OAR dose constraint violation; (4) imaging modalities: orthogonal kV imaging verifies bony anatomy but cannot detect soft tissue changes, CBCT provides volumetric anatomy but has limited Hounsfield unit accuracy for proton range recalculation, fan-beam CT-on-rails offers superior Hounsfield unit fidelity for range verification, synthetic CT generated from CBCT is an emerging alternative; (5) online adaptive proton therapy—plan modification immediately before each fraction—requires fast CT imaging, rapid Monte Carlo dose calculation, and streamlined QA, and remains available at a limited number of specialist centers.

4. Clinical Evidence by Disease Site

An important caveat applies to all clinical evidence reviewed in this section: no randomized or prospective comparative trial has demonstrated superiority or confirmed equivalence of proton versus photon therapy for locoregional control, progression-free survival, or overall survival in any gynecological malignancy. Available dosimetric data confirm that IMPT achieves comparable target coverage metrics (V95%, D99%) to IMRT, providing dosimetric—but not clinical—evidence of equivalent tumor dose delivery. The biological equivalence assumption (RBE = 1.1) implies similar expected cell kill for equivalent physical doses, but this assumption carries uncertainty, particularly at distal field edges. All statements regarding clinical benefit in this section reflect early, preliminary data and are subject to prospective validation. Ongoing trials—PROTECT and APROVE—should incorporate locoregional control and survival as secondary endpoints to begin addressing this critical evidence gap.

4.1. Cervical Cancer

4.1.1. Background and Treatment Paradigms

Cervical cancer remains a leading cause of cancer-related mortality in women worldwide, particularly in resource-limited settings [36]. Standard treatment for locally advanced cervical cancer (LACC) consists of concurrent chemoradiation followed by image-guided brachytherapy boost [36]. For early-stage disease with high-risk features, postoperative pelvic radiation with or without chemotherapy is indicated. The proximity of cervical tumors to bladder, rectum, sigmoid colon, and small bowel makes this an ideal disease site for exploring the potential benefits of proton therapy [37].

4.1.2. Definitive Treatment Setting

The evidence for proton therapy in the definitive treatment of cervical cancer consists primarily of dosimetric planning studies and small clinical series. Kagei et al. reported long-term results of proton beam therapy for carcinoma of the uterine cervix in an early series from Japan, though detailed outcome data are limited in the available literature [38]. This pioneering work established the feasibility of proton therapy for cervical cancer but predated modern IMPT techniques.

Multiple planning studies have demonstrated substantial dosimetric advantages for IMPT in the definitive setting. Marnitz et al. showed that IMPT reduced small-bowel mean dose by 38–52% compared to photon techniques for both pelvic and extended-field irra-

diation in 20 patients with FIGO stage IB2-IVA cervical cancer [23]. All techniques provided excellent target volume coverage, homogeneity, and conformity, but protons offered superior OAR sparing that the authors suggested could contribute to significant reductions in acute and late toxicity [23].

Critical point: Image-guided brachytherapy (IGBT) is and must remain the irreplaceable standard of care for the boost component of definitive cervical cancer treatment. No external beam technique, including IMPT, should substitute for IGBT in anatomically eligible patients. Georg et al.'s benchmark study demonstrated inferior gross tumor volume coverage (lower D90) and less favorable dose distributions with both IMPT and IMRT versus high-tech brachytherapy in nine patients [4]. The dosimetric superiority of IGBT reflects the fundamental geometric advantage of intracavitary dose delivery that beam quality improvements cannot overcome. Proton therapy must therefore be understood as strictly complementary to brachytherapy, not as a replacement. External beam boost with IMPT represents a second-line option reserved for the minority of patients in whom brachytherapy is anatomically or medically contraindicated.

For patients unable to receive brachytherapy due to anatomical constraints or other factors, an external beam boost may be necessary. Sharma et al. compared pencil-beam scanning with photon-based SBRT for boost treatment in five patients, demonstrating that PBS significantly reduced integral dose to normal tissues (14.17 ± 2.65 Gy vs. 25.29 ± 6.35 Gy for IMRT and 25.24 ± 6.24 Gy for VMAT) and achieved lower maximum doses to bladder and rectum [30]. While these dosimetric advantages are encouraging, clinical validation of outcomes is needed [30].

4.1.3. Postoperative Setting

The postoperative setting represents a particularly promising application for proton therapy, as target volumes are typically well-defined and the absence of gross disease may reduce concerns about range uncertainties. Lin et al. reported the initial clinical experience with pencil-beam scanning proton therapy for 11 posthysterectomy patients with gynecologic cancer (seven cervical, three endometrial, one vaginal) receiving whole pelvis radiation therapy [34]. All patients completed treatment to 45–50.4 Gy[RBE]. Among nine patients receiving concurrent chemotherapy, Grade 2 and 3 hematologic toxicities occurred in 33% and 11%, respectively, and Grade 3 acute gastrointestinal toxicity occurred in 9% of patients. No patient developed Grade ≥3 genitourinary toxicity [34]. These toxicity rates compare favorably to historical photon series, though direct comparative data are limited.

Dosimetric analysis in the Lin et al. series confirmed that PBS significantly lowered the volume of pelvic bone marrow, bladder, and small bowel receiving 10 to 30 Gy compared to IMRT ($p < 0.05$), while rectum dose was comparable [35]. Target coverage robustness was maintained under simulated setup uncertainties, supporting the clinical feasibility of PBS in this setting [34].

4.1.4. Extended-Field Nodal Irradiation

Extended-field radiation therapy, including para-aortic lymph nodes, is indicated for patients with documented para-aortic nodal involvement or high risk of occult disease. The large treatment volumes involved in EFRT result in substantial normal tissue exposure with photon techniques, making this a particularly attractive application for proton therapy.

Marnitz et al. specifically evaluated EFRT in 10 patients, demonstrating that IMPT reduced small-bowel mean dose from 24.0 to 26.3 Gy with photon techniques to 13.8 Gy, a reduction of approximately 47% [23]. The low-dose bath (V10Gy) to the small bowel was reduced by approximately 50%, which may be particularly relevant for reducing acute gastrointestinal toxicity during concurrent chemotherapy [23]. These dosimetric ad-

vantages suggest that proton therapy may enable safer delivery of EFRT, potentially expanding treatment options for patients with advanced nodal disease.

4.1.5. Survival and Quality of Life Outcomes

A critical gap in the cervical cancer proton therapy literature is the paucity of long-term survival and quality of life data from prospective trials. Most published series focus on dosimetric comparisons or short-term toxicity outcomes. The PROTECT trial, a prospective phase II multicenter study evaluating adaptive IMPT for locally advanced cervical cancer, aims to address this gap [38]. The trial includes 30 women receiving external beam radiation therapy with concurrent chemotherapy and 3D image-guided adaptive brachytherapy. Primary endpoints include pelvic bone mean dose and mean bowel V15Gy, with secondary endpoints encompassing dosimetric parameters, oncological outcomes, health-related quality of life, immune response, safety, and tolerability [38]. Results from this trial will provide the first prospective data on the potential of IMPT to reduce OAR dose and improve toxicity and quality of life for patients with locally advanced cervical cancer. No locoregional control, progression-free survival, or overall survival data comparing proton versus photon therapy in cervical cancer are currently available from prospective studies. The evidence reviewed here is entirely dosimetric or short-term toxicity-based. Future studies must include oncologic efficacy endpoints as co-primary or key secondary outcomes alongside toxicity and quality of life measures, so that the role of proton therapy in cervical cancer can be definitively established.

4.2. Endometrial Cancer

4.2.1. Clinical Context and Treatment Indications

Endometrial cancer is the most common gynecologic malignancy in developed countries, with most patients presenting with early-stage disease [35]. Adjuvant radiation therapy is indicated for patients with high-risk features, including deep myometrial invasion, lymphovascular space invasion, high-grade histology, or lymph node involvement [35]. Treatment typically consists of vaginal brachytherapy alone for intermediate-risk disease or whole pelvic radiation therapy (with or without vaginal brachytherapy boost) for high-risk or node-positive disease [39]. Extended-field radiation, including para-aortic nodes, may be indicated for patients with documented para-aortic nodal involvement [39].

4.2.2. Comparative Clinical Outcomes

The most robust clinical evidence for proton therapy in endometrial cancer comes from a prospective registry study by Anderson et al. comparing patient-reported outcomes in 67 patients (22 proton therapy, 45 IMRT) receiving adjuvant pelvic radiation therapy [4,5]. This study employed the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) to assess symptoms during and after treatment. The patient selection process and the specific allocation into the Proton ($n = 22$) and IMRT ($n = 45$) cohorts are detailed in the CONSORT flow diagram [Figure 5].

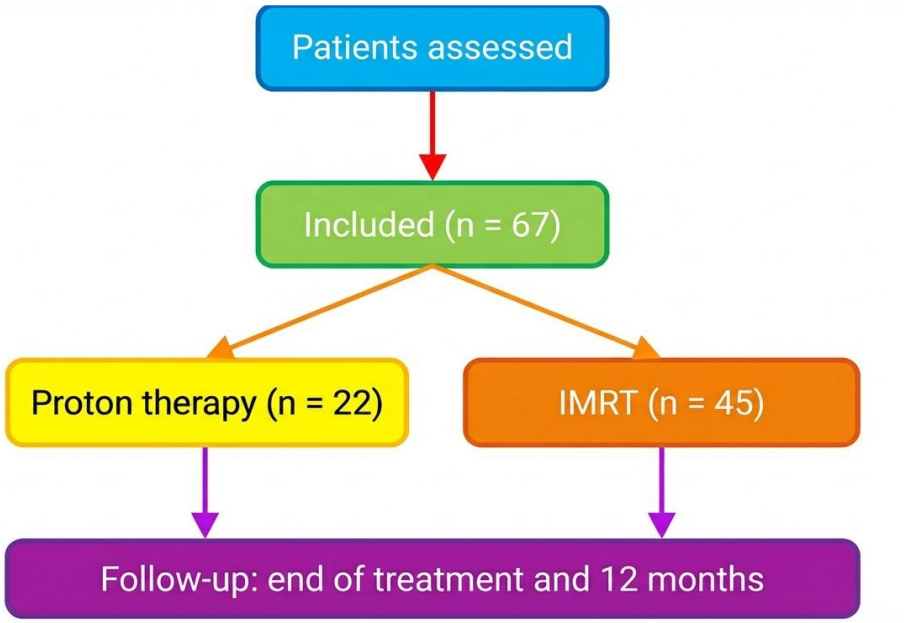

Figure 5. CONSORT flow diagram of patient selection and study design. This flowchart details the recruitment and enrollment process for the 67 patients analyzed in the prospective registry study. Subjects were allocated into either the Proton Therapy cohort (n = 22) or the IMRT cohort (n = 45) based on treatment modality. The diagram outlines the clinical pathway from initial screening through the 12-month follow-up period used to evaluate patient-reported outcomes and clinician-graded toxicities. Created in BioRender. Bakshi H (2026) https://BioRender.com/basic.

Proton therapy was associated with significantly less diarrhea at the end of treatment compared to IMRT ($p = 0.01$), with a trend toward less diarrhea persisting at 12 months ($p = 0.24$) [4,5]. Loss of bowel control at 12 months was more common with IMRT ($p = 0.15$), suggesting potential long-term functional benefits with proton therapy [4,5]. Clinician-graded Grade 3+ gastrointestinal toxicity was noted more frequently with IMRT (31% vs. 9%, $p = 0.09$), though this difference did not reach statistical significance in this relatively small cohort [4,5]. As illustrated in Figure 6, while the cohort size was limited, the divergence in severe gastrointestinal complications between treatment modalities suggests a notable clinical advantage for proton therapy.

These patient-reported outcome data are particularly valuable as they capture the patient experience of treatment-related symptoms, which may be more sensitive to differences in treatment modality than clinician-graded toxicity scales. The findings suggest that the dosimetric advantages of proton therapy translate into meaningful improvements in gastrointestinal symptoms and bowel function, though longer follow-up and larger cohorts are needed to confirm these results and assess late toxicity and survival outcomes [4,5]. However, it must be noted that the Anderson et al. registry study was designed to assess patient-reported toxicity, not oncologic efficacy. No prospective data on locoregional control, recurrence rates, or survival comparing proton versus photon therapy in endometrial cancer are available. Future comparative studies must incorporate tumor control endpoints as co-primary or key secondary outcomes.

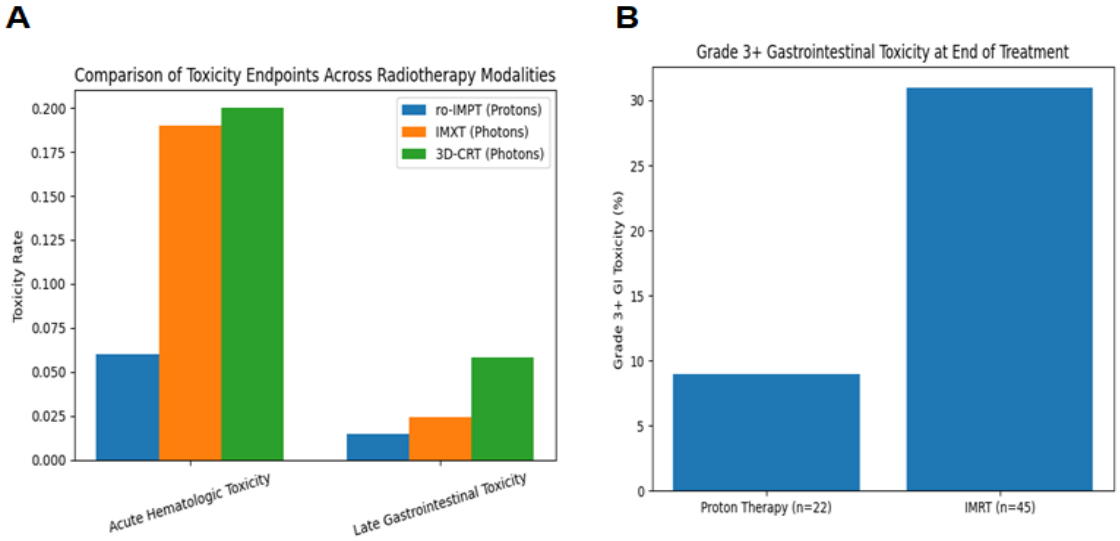

Figure 6. Comparative analysis of acute and late gastrointestinal toxicity. (**A**) Modality Comparison: Estimated toxicity risks across three treatment modalities: robustly optimized intensity-modulated proton therapy (ro-IMPT), intensity-modulated X-ray therapy (IMXT), and 3D-conformal radiation therapy (3D-CRT). (**B**) Clinical Outcomes: Observed percentage of Grade 3+ gastrointestinal (GI) toxicity at the conclusion of treatment. In the clinical registry study, proton therapy demonstrated a marked reduction in severe GI complications (9%) compared to IMRT (31%). Created in BioRender. Bakshi H. (2026) https://BioRender.com/basic.

4.2.3. Extended-Field Radiation for Node-Positive Disease

Xu et al. evaluated extended-field radiation for 25 patients with locally advanced endometrial malignancies (seven treated with PBS, 18 with IMRT), focusing on pelvic and para-aortic lymph node disease [25]. PBS resulted in 22% lower median pelvic bone marrow volume irradiated to 10 Gy[RBE] (71.3% vs. 93.4%, $p < 0.001$), with significantly lower dose volumes across the range from 0 to 26 Gy [25]. PBS also achieved significantly lower doses to the small bowel, large bowel, and bladder in the lower dose regions [25].

These dosimetric advantages are particularly relevant for extended-field treatments where large volumes of bone marrow and bowel are at risk. The substantial reduction in bone marrow exposure may enable better tolerance of concurrent chemotherapy and preserve immune function, though clinical validation of these hypothesized benefits is needed.

4.2.4. Postoperative Pelvic Radiation

Wark et al. conducted a matched-pair cohort study specifically evaluating bone marrow sparing in postoperative irradiation of gynecologic malignancies, including 17 endometrial cancer patients among 50 total patients (25 IMPT, 25 IMRT) [31]. IMPT significantly reduced integral dose to the pelvic skeleton (23.4 Gy[RBE] vs. 34.3 Gy, $p < 0.001$) and achieved 40–41% reductions in V5Gy and V10Gy to the pelvic skeleton [31]. This translated into significantly less hematotoxicity in the IMPT group (32% vs. 80%, $p = 0.0009$), with particularly striking reductions in Grade ≥2 hematotoxicity (8% vs. 36%, $p = 0.037$) [31]. No patient in the IMPT group experienced hematotoxicity greater than Grade 2 [31].

Interestingly, the study also reported sacral insufficiency fractures in 32% of IMPT patients, appearing similar to reported IMRT rates [31]. These findings highlight that while proton therapy reduces integral bone dose, it does not eliminate the risk of bone-related complications, and attention to bone health remains important.

4.3. Ovarian Cancer

Limited Evidence Base

The role of radiation therapy in ovarian cancer is limited compared to cervical and endometrial cancers, as systemic therapy is the primary treatment modality for most patients [40]. Radiation may be considered for consolidation after chemotherapy in selected patients with limited residual disease, palliation of symptomatic metastases, or treatment of isolated recurrences. Consequently, the literature on proton therapy for ovarian cancer is extremely sparse [41].

No dedicated clinical series or outcomes data for proton therapy in ovarian cancer were identified in the current literature review. The potential applications of proton therapy in this disease site remain largely theoretical, based on extrapolation from other gynecologic malignancies [42]. Whole abdominal radiation, historically used for ovarian cancer, would theoretically benefit from proton therapy's reduced integral dose and low-dose bath, potentially reducing toxicity to liver, kidneys, and bone marrow [42]. However, the large treatment volumes, respiratory motion, and range uncertainties present significant technical challenges.

For patients with isolated pelvic or para-aortic nodal recurrences, proton therapy might offer advantages similar to those demonstrated in cervical and endometrial cancers, with improved OAR sparing enabling safer dose escalation or reirradiation [43]. However, clinical data are needed to validate these hypothetical benefits.

4.4. Vaginal and Vulvar Cancers

4.4.1. Clinical Context

Vaginal and vulvar cancers are rare gynecologic malignancies, collectively accounting for less than 10% of gynecologic cancers [44]. Treatment typically involves surgery and/or radiation therapy, with the specific approach depending on stage, location, and patient factors [44]. Radiation therapy plays a central role in organ preservation strategies and for locally advanced disease [45]. The proximity of treatment volumes to critical structures, including the urethra, bladder, rectum, and anal sphincter, makes toxicity a significant concern [45].

Across the disease sites discussed above, a consistent pattern emerges: dosimetric advantages of proton therapy are well-documented, while clinical outcome data remain limited to small retrospective series, matched cohorts, and a single prospective registry study. Table 2 consolidates the key studies reviewed in this section, summarizing study design, disease site, patient population, comparator technique, and principal dosimetric and clinical findings. This summary highlights both the breadth of dosimetric evidence accumulated to date and the corresponding scarcity of prospective comparative data, underscoring the need for the randomized trials discussed in subsequent sections of this review.

Table 2. Summary of key studies evaluating proton beam therapy in gynecological malignancies.

Study (Ref.)	Design	Disease Site/Setting	n	Comparator	Key Dosimetric Finding	Key Clinical Finding
Marnitz et al. [23]	Intra-patient planning study	Cervical cancer; pelvic and extended-field (EFRT)	20	IMPT vs. IMRT, helical tomotherapy, VMAT	Mean small-bowel dose ↓38–52%; V10Gy ↓~50%; bladder/rectum dose ↓7–9 Gy	Dosimetric only; clinical validation not performed

Boer et al. [27]	Planning study with MRI-based target tailoring	Cervical cancer; definitive setting	11	IMPT vs. IGART (photon adaptive)	NTCP for Grade ≥2 acute small-bowel toxicity reduced from 25% (IGART) to 18% (IMPT alone) to 9% (IMPT + tailoring)	In silico NTCP modeling only
Hashimoto et al. [28]	Planning study	Cervical cancer; whole-pelvis RT	10	Spot-scanning proton therapy (SSPT) vs. IMRT and 3D-CRT	Lower median small intestine V20; favorable homogeneity/conformity indices	Dosimetric only
Shang et al. [29]	Robust optimization planning study	Cervical cancer	18	Robustly optimized IMPT vs. helical IMRT	DVH band widths 0.6% (IMPT) vs. 2.1% (IMRT); NTCP rectum 2.8% vs. 4.8% ($p < 0.05$); sigmoid 5.2% vs. 5.7% ($p < 0.05$)	Dosimetric/NTCP modeling only
Sharma et al. [30]	Planning study (boost comparison)	Cervical cancer; boost for brachytherapy-ineligible patients	5	Pencil-beam scanning (PBS) vs. photon-based SBRT (IMRT/VMAT)	Integral dose 14.17 ± 2.65 Gy (PBS) vs. 25.29 ± 6.35 Gy (IMRT)/25.24 ± 6.24 Gy (VMAT); lower max bladder/rectum dose	Dosimetric only; clinical validation needed
Georg et al. [4]	Benchmark planning comparison	Cervical cancer; brachytherapy boost	9	IMRT and IMPT vs. high-tech image-guided brachytherapy (IGBT)	Both IMRT and IMPT show lower GTV D90 and less favorable dose distributions vs. IGBT	Confirms IGBT remains the gold standard; proton therapy is complementary, not a replacement
Wark et al. [31]	Matched-pair cohort study	Cervical and endometrial cancer; postoperative pelvic RT	50 (25 IMPT, 25 IMRT)	IMPT vs. IMRT	Integral pelvic skeletal dose 23.4 Gy[RBE] (IMPT) vs. 34.3 Gy (IMRT), $p < 0.001$; V5Gy/V10Gy ↓40–41%	Any-grade hematotoxicity 32% vs. 80% ($p = 0.0009$); Grade ≥2 hematotoxicity 8% vs. 36% ($p = 0.037$); sacral insufficiency fractures 32% (IMPT), similar to IMRT
Xu et al. [25]	Retrospective planning comparison	Endometrial cancer; extended-field nodal RT	25 (7 PBS, 18 IMRT)	PBS vs. IMRT	Median pelvic bone marrow V10Gy[RBE] 71.3% (PBS) vs.	Dosimetric only; clinical validation needed

					93.4% (IMRT), $p < 0.001$; lower-small-bowel, large-bowel, bladder doses at low-dose regions	
Song et al. [33]	Planning comparison	Cervical cancer; pelvic bone marrow sparing	Not specified	3D conformal proton therapy (3DCPT) vs. IMRT	3DCPT superior for V10/V20 (↓10.8% and ↓7.4%, p = 0.001/0.04); IMRT better for V30+	Dosimetric only
Lin et al. [34]	Prospective clinical feasibility series	Cervical (7), endometrial (3), vaginal (1) cancer; postoperative whole pelvis RT	11	PBS proton therapy vs. historical IMRT series	PBS significantly lowered pelvic bone marrow, bladder, and small-bowel dose (10–30 Gy) vs. IMRT ($p < 0.05$); rectum dose comparable; target coverage robust	Grade 2/3 hematologic toxicity 33%/11%; Grade 3 GI toxicity 9%; no Grade ≥3 GU toxicity (9 patients with concurrent chemo)
Yoshimura et al. [3]	Robust optimization planning + NTCP modeling	Mixed gynecologic malignancies; postoperative whole pelvic RT	13	ro-IMPT vs. 3D-CRT and IMXT	Median NTCP acute hematologic toxicity: 0.06 (ro-IMPT) vs. 0.20 (3D-CRT) vs. 0.19 (IMXT); late GI NTCP: 0.015 vs. 0.058 vs. 0.024	In silico modeling only
Anderson et al. [4,5]	Prospective registry study (PRO-CTCAE)	Endometrial cancer; adjuvant pelvic RT	67 (22 proton, 45 IMRT)	Proton therapy vs. IMRT	Not primary endpoint (clinical registry)	Less diarrhea at the end of treatment (p = 0.01); Grade 3+ GI toxicity 9% (proton) vs. 31% (IMRT), p = 0.09 (NS); the strongest available prospective clinical evidence
PROTECT trial [35] (ongoing)	Prospective phase II multicenter trial	Locally advanced cervical cancer	30 (planned)	Adaptive IMPT vs. IMRT/VMAT	Primary endpoints: pelvic bone mean dose, bowel V15Gy	Secondary endpoints: oncological outcomes, QoL, immune response, safety, tolerability—results pending

APROVE trial [46] (ongoing)	Prospective phase II single-arm trial	Cervical and endometrial cancer; postoperative pelvic RT	25 (planned)	Proton therapy (single arm)	Planning study: significant ↓ small/large-bowel and kidney dose vs. photon; PBS reduced bowel V15 vs. IMRT	Primary endpoint: absence of CTCAE Grade 3/4 toxicity; secondary: QoL (EORTC-QLQ30/-EN24/-CX24), PFS—results pending

Note: ↓ This symbol indicates decrease. Abbreviations: IMPT, intensity-modulated proton therapy; PBS, pencil-beam scanning; ro-IMPT, robustly optimized IMPT; IMRT, intensity-modulated radiation therapy; VMAT, volumetric modulated arc therapy; 3D-CRT, three-dimensional conformal radiotherapy; IMXT, intensity-modulated X-ray therapy; IGART, image-guided adaptive radiation therapy; IGBT, image-guided brachytherapy; NTCP, normal tissue complication probability; GTV, gross tumor volume; GI, gastrointestinal; GU, genitourinary; QoL, quality of life; PFS, progression-free survival; NS, not significant. Most studies represent dosimetric planning comparisons or small retrospective/prospective cohorts; no randomized controlled trial data are currently available.

4.4.2. Limited Clinical Experience

The literature on proton therapy for vaginal and vulvar cancers is extremely limited. Lin et al. included one vaginal cancer patient in their series of 11 posthysterectomy patients receiving PBS proton therapy [34]. Site-specific toxicity outcomes were not separately reported for this patient, limiting conclusions about the specific benefits in vaginal cancer.

No dedicated series of proton therapy for vulvar cancer was identified in the current literature review [47]. The superficial location of vulvar tumors and the need for adequate skin dose present unique challenges for proton therapy, as the Bragg peak must be positioned to ensure adequate dose at shallow depths [47]. Additionally, the proximity to critical structures, including the urethra, vagina, and anal sphincter, requires careful treatment planning [48].

Despite the limited evidence, there are theoretical rationales for considering proton therapy in selected cases of vaginal and vulvar cancer [49]. For vaginal cancers requiring pelvic nodal irradiation, the dosimetric advantages demonstrated for cervical cancer would likely apply [49]. For vulvar cancers requiring inguinal and pelvic nodal irradiation, proton therapy might reduce dose to femoral heads, external genitalia, and pelvic organs, potentially reducing both acute and late toxicity [49]. However, clinical data are urgently needed to validate these theoretical benefits and establish appropriate patient selection criteria.

5. Special Clinical Scenarios

5.1. Postoperative Pelvic Irradiation

Postoperative pelvic radiation represents a particularly promising application of proton therapy. As detailed in Sections 3.5, 4.1.3 and 4.2.4, dosimetric advantages and favorable early clinical outcomes have been demonstrated by Lin et al. [34], Wark et al. [31], and Yoshimura et al. [3]. The ongoing APROVE trial will provide prospective phase II evidence for this setting [46].

5.2. Extended-Field Nodal Treatment

The dosimetric advantages of proton therapy are particularly pronounced for extended-field treatments, as demonstrated by Marnitz et al. (~47% small-bowel dose reduc-

tion) and Xu et al. (22% lower pelvic bone marrow V10Gy[RBE]), detailed in Sections 4.1.4 and 4.2.3, respectively [23,25]. These advantages may enable safer EFRT delivery for patients with advanced nodal disease [50].

5.3. Reirradiation for Recurrent Disease

Reirradiation for recurrent gynecological malignancies represents one of the most challenging scenarios in radiation oncology [51]. Patients with pelvic recurrences after prior radiation therapy have limited treatment options, and reirradiation with conventional photon techniques carries substantial risks of severe late toxicity due to cumulative dose to previously irradiated normal tissues [52]. The ability of proton therapy to minimize dose to surrounding normal tissues while delivering adequate dose to the recurrent tumor makes it an attractive option in this setting [53].

Despite the theoretical advantages, the current literature on proton therapy for reirradiation of gynecological malignancies is extremely limited [11]. No dedicated clinical series or outcomes data were identified in the current review. This represents a significant evidence gap, as reirradiation is a clinical scenario where proton therapy might offer the greatest potential benefit [54].

The challenges of reirradiation with proton therapy include accurate assessment of prior dose distributions (particularly if prior treatment was delivered at a different institution or with older techniques), accounting for tissue changes from prior radiation and surgery, managing range uncertainties in previously irradiated tissues, and predicting cumulative toxicity risks [55,56]. Advanced imaging, including MRI and PET, may help define target volumes and assess tissue changes, while sophisticated dose accumulation techniques can estimate cumulative dose distributions [57].

Future research should prioritize evaluation of proton therapy for reirradiation in gynecological malignancies, including development of patient selection criteria, dose-fractionation strategies, and systematic assessment of outcomes and toxicity [58]. Registry studies or multi-institutional collaborations may be necessary to accrue sufficient patients, given the relative rarity of this clinical scenario [58].

6. Integration with Systemic Therapies

6.1. Concurrent Chemotherapy

Concurrent chemoradiation is the standard of care for locally advanced cervical cancer and is increasingly used for high-risk endometrial cancer [59]. The radiosensitizing chemotherapy, typically cisplatin-based, enhances tumor cell kill but also increases acute toxicity, particularly hematologic and gastrointestinal effects [59]. The potential for proton therapy to reduce bone marrow and bowel dose may enable better tolerance of concurrent chemotherapy, potentially allowing for improved treatment compliance and dose intensity [59].

Clinical experience with proton therapy and concurrent chemotherapy in gynecological malignancies is limited but growing. Lin et al. reported that among 11 posthysterectomy patients receiving PBS proton therapy, nine received concurrent chemotherapy (typically cisplatin) [8]. Among these nine patients, Grade 2 and 3 hematologic toxicities occurred in 33% and 11%, respectively, and Grade 3 acute gastrointestinal toxicity occurred in 9% [8]. No patient developed Grade ≥3 genitourinary toxicity [8]. While these rates compare favorably to historical photon series, direct comparative data are limited.

Wark et al. demonstrated that IMPT significantly reduced hematotoxicity compared to IMRT in postoperative irradiation of gynecologic malignancies (32% vs. 80%, $p = 0.0009$), with particularly striking reductions in Grade ≥2 hematotoxicity (8% vs. 36%, $p = 0.037$) [31]. This reduction in hematologic toxicity may be particularly relevant for patients re-

ceiving concurrent chemotherapy, potentially allowing for better treatment compliance and reduced need for dose modifications or treatment breaks. However, as discussed in Section 3.4, reported hematotoxicity differences between proton and photon chemoradiation cohorts may be partially attributable to differences in bone marrow contouring methodology, radiation field extent, cisplatin dose intensity, and baseline patient characteristics, rather than radiation modality alone. These confounders should be addressed in the design and reporting of future comparative studies.

The PROTECT trial is specifically evaluating adaptive IMPT for locally advanced cervical cancer with concurrent chemotherapy, with endpoints including not only dosimetric parameters and toxicity but also immune response [35]. This is particularly relevant as emerging evidence suggests that radiation-induced lymphopenia may impact outcomes, and preservation of circulating lymphocytes through reduced dose to the blood pool and bone marrow may be beneficial.

6.2. Targeted Therapies and Immunotherapy

The integration of targeted therapies and immunotherapy with radiation therapy represents an evolving frontier in oncology [60]. For gynecological malignancies, targeted agents including bevacizumab (anti-VEGF antibody) and PARP inhibitors are increasingly used, while immune checkpoint inhibitors are being evaluated in selected populations, including mismatch repair-deficient endometrial cancers and PD-L1-positive cervical cancers [60].

The potential synergy between proton therapy and immunotherapy is an area of active investigation [61]. Radiation therapy can enhance anti-tumor immunity through multiple mechanisms, including induction of immunogenic cell death, upregulation of tumor antigens, and modulation of the tumor microenvironment. However, radiation can also suppress immune function through lymphopenia induced by irradiation of circulating lymphocytes and bone marrow [61].

Proton therapy's ability to reduce the low-dose bath and spare bone marrow may preserve immune function better than photon therapy, potentially enhancing the efficacy of immunotherapy combinations. Kuipers et al. developed a dynamic lymphocyte flow model to predict lymphocyte dose and surviving fraction for VMAT and IMPT treatments in locally advanced cervical cancer [62]. While specific results are not detailed in the available metadata, this type of modeling may help optimize radiation techniques to minimize immunosuppression.

The PROTECT trial includes immune response as a secondary endpoint, which will provide valuable data on the impact of IMPT versus IMRT/VMAT on immune function in cervical cancer patients [35]. However, clinical trials specifically evaluating proton therapy in combination with immunotherapy or targeted agents for gynecological malignancies are lacking, representing an important area for future research.

6.3. Sequencing and Timing Considerations

The optimal sequencing and timing of proton therapy with systemic therapies remain to be fully defined. For concurrent chemoradiation, the approach is similar to photon therapy, with chemotherapy delivered weekly during radiation [63]. For sequential approaches, considerations include the potential for proton therapy to reduce cumulative toxicity when combined with prior or subsequent chemotherapy, the impact of systemic therapy on tissue composition and range uncertainties, and the timing of adaptive replanning if significant anatomical changes occur during treatment [44].

Future research should address these sequencing questions through prospective trials, with careful attention to pharmacokinetic interactions, toxicity profiles, and efficacy outcomes. The development of predictive biomarkers to identify patients most likely to

benefit from proton therapy in combination with specific systemic agents would facilitate personalized treatment approaches [64].

7. Adaptive Treatment Strategies and Image-Guided Approaches

7.1. Rationale for Adaptive Proton Therapy

Gynecological malignancies present unique challenges for radiation therapy due to significant interfractional anatomical variations. Bladder and rectal filling, bowel motion, tumor response during treatment, and weight changes can all impact target position and normal tissue anatomy [65]. For proton therapy, these anatomical changes are particularly problematic due to range uncertainties—small changes in tissue density or patient positioning can significantly alter the proton beam range and dose distribution [65].

Adaptive radiation therapy (ART) involves systematic monitoring of anatomical changes during treatment and modification of the treatment plan when necessary to maintain optimal target coverage and OAR sparing [66]. For proton therapy, adaptive approaches are not merely beneficial but may be essential to realize the full potential of the modality while ensuring safe and effective treatment delivery [66].

7.2. MRI-Guided Target Tailoring

Boer et al. investigated the combination of MRI-based target tailoring and proton therapy for cervical cancer, demonstrating synergistic benefits [27]. The study included planning CTs from 11 previously treated cervical cancer patients who had a >4 cm tumor-free part of the proximal uterus on diagnostic MRI. Four treatment plans were compared per patient: standard target with image-guided adaptive radiation therapy (IGART) alone, standard target with IMPT, tailored target (excluding tumor-free proximal uterus) with IGART, and tailored target with IMPT [27].

IMPT alone reduced the NTCP for Grade ≥2 acute small-bowel toxicity from 25% to 18%, while combining IMPT with MRI-based target tailoring further reduced NTCP to 9% [27]. The study found that NTCP reductions exceeding 10% could be achieved if V45Gy for bowel bag was >275 cm^3 with IMPT alone or >200 cm^3 with IMPT plus tailoring [27]. IMPT significantly reduced V15Gy, V30Gy, V45Gy, and mean dose for bladder and small bowel [27].

This study demonstrates that adaptive target tailoring based on advanced imaging can complement the physical advantages of proton therapy, achieving toxicity reductions that exceed what either approach can accomplish alone. The integration of MRI into proton therapy workflows, while technically challenging, may be essential for optimal outcomes in gynecological malignancies.

7.3. Robust Optimization Strategies

Robust optimization is a treatment planning technique that explicitly accounts for uncertainties in patient setup, organ motion, and proton range by optimizing the plan to maintain acceptable target coverage and OAR sparing across a range of uncertainty scenarios [67]. This approach is particularly important for proton therapy, where dose distributions are more sensitive to uncertainties than photon therapy [67].

Shang et al. compared robustly optimized IMPT with helical IMRT for cervical cancer in 18 patients, demonstrating that robust optimization yielded smaller dose-variation bands under perturbed scenarios and more stable target coverage [29]. The study found that robustly optimized IMPT achieved better CTV coverage and OAR sparing with smaller DVH band widths (0.6% vs. 2.1%) compared to IMRT [5]. NTCP calculations revealed lower toxicities for robustly optimized IMPT: rectum 2.8% vs. 4.8% ($p < 0.05$) and sigmoid 5.2% vs. 5.7% ($p < 0.05$) [29].

Yoshimura et al. specifically evaluated robustly optimized IMPT (ro-IMPT) for post-operative whole pelvic radiotherapy, demonstrating significant reductions in NTCP for acute hematologic toxicity and late gastrointestinal toxicity compared with 3D-CRT and IMXT [3]. The robust optimization approach ensured that these benefits were maintained even in the presence of setup and range uncertainties [3].

7.4. Image-Guided Radiation Therapy

Practical IGRT Workflow in Gynecological Proton Therapy

Daily image guidance serves three functions in proton therapy: (1) positioning verification—correcting translational and rotational setup errors; (2) anatomy assessment—detecting significant interfractional anatomical changes; and (3) range verification—confirming the beam stops at the intended depth. Orthogonal kV imaging verifies bony alignment but cannot detect soft tissue filling changes. CBCT provides volumetric soft tissue imaging but has limited Hounsfield unit accuracy for direct proton range recalculation. Fan-beam CT-on-rails offers superior Hounsfield unit fidelity and is preferred for range verification when available. Emerging approaches include synthetic CT generation from CBCT for online range verification. Adaptive replanning is triggered when daily imaging reveals anatomy deviating beyond predefined thresholds: CTV centroid shift >3 mm, D95 target coverage <95%, or OAR constraint violation. Offline adaptation prepares a revised plan between fractions; online adaptation modifies the plan at the machine immediately before treatment delivery, requiring fast dose calculation and streamlined QA. MRI guidance—established for photon MR-linac platforms—remains aspirational for proton therapy with prototype systems under development.

The PROTECT trial is evaluating adaptive proton therapy for cervical cancer with a systematic assessment of anatomical changes and plan adaptation [35]. The trial protocol includes 3D image-guided adaptive brachytherapy in addition to external beam proton therapy, recognizing the importance of image guidance throughout the treatment course [35].

Future developments in image-guided proton therapy may include MRI-linear accelerator (MR-linac) analogs for protons, real-time tumor tracking, and automated plan adaptation algorithms. These technologies could further enhance the precision and safety of proton therapy for gynecological malignancies, though significant technical challenges remain.

7.5. Brachytherapy Integration

Image-guided brachytherapy (IGBT) remains the irreplaceable standard boost modality for eligible cervical cancer patients, and this must be stated explicitly when discussing any external beam alternative. Georg et al.'s benchmark study confirmed that IMPT, despite its physical advantages, achieves inferior gross tumor volume D90 and less favorable dose–volume distributions compared to IGBT [4]. External beam proton boost is a second-line option strictly for brachytherapy-ineligible patients. Careful dose accumulation accounting for anatomical changes between external beam and brachytherapy phases is required when combining both modalities [31]. The PROTECT trial evaluates IMPT integrated with 3D image-guided adaptive brachytherapy—the appropriate combined approach [35].

8. Current Limitations and Challenges

8.1. Cost and Economic Considerations

The high capital and operational costs of proton therapy represent a major barrier to widespread adoption [68]. Proton therapy centers require substantial infrastructure, in-

cluding cyclotrons or synchrotrons, beam transport systems, treatment gantries, and sophisticated treatment planning and quality assurance systems [68]. The initial capital investment for a multi-room proton therapy center typically ranges from $100–200 million, with ongoing operational costs significantly exceeding those of conventional photon therapy facilities [68].

According to market analyses, the global proton therapy market was valued at approximately $763.6 million in 2023 and is projected to grow to $2405.6 million by 2032, with a compound annual growth rate of 12.11% [69]. Despite this growth, proton therapy remains accessible to less than 9% of patients who would potentially benefit from it. The limited number of proton therapy centers worldwide, concentrated primarily in high-income countries, creates geographic barriers to access [69].

Current evidence does not justify the routine broad implementation of proton therapy for all gynecological cancer patients. Given that IMPT typically costs approximately 2–3 times more per fraction than IMRT, the economic case requires demonstrable reductions in hospitalization rates, interventional procedures, and long-term complication management—none of which have been prospectively established in this disease site. A model-based patient selection framework—analogous to that proposed for head and neck and prostate cancers—offers a rational interim approach: selecting patients whose NTCP analysis predicts a clinically meaningful benefit threshold (e.g., >10% absolute NTCP reduction) with proton versus photon plans. This strategy concentrates the resource investment where clinical benefit is most probable while the evidence base matures. Development of compact, lower-cost single-room proton systems may substantially reduce the economic barrier [70].

8.2. Limited Accessibility and Geographic Disparities

As of 2024, there were approximately 40 operational proton therapy centers in the United States and fewer than 100 worldwide [71]. This limited availability creates substantial geographic disparities in access, with patients in rural areas or developing countries having little to no access to proton therapy. Even in countries with multiple centers, the concentration of facilities in urban areas means that many patients face significant travel burdens, including time away from work and family, lodging costs, and logistical challenges [71].

The 2025 NAPT survey reported that two new proton therapy centers came online in 2024 in North Carolina and Illinois, modestly expanding access [71,72]. However, the rate of new center development has slowed compared to earlier years, partly due to economic pressures and uncertainty about reimbursement. The number of patients receiving proton therapy increased by only 1081 patients from 2023 to 2024, totaling 18,202 nationwide, a modest increase that reflects both capacity constraints and referral patterns [71].

For gynecological malignancies specifically, the limited evidence base and lack of clear clinical guidelines contribute to underutilization even among patients with geographic access to proton therapy [11]. Many radiation oncologists and gynecologic oncologists remain unfamiliar with the potential benefits and appropriate patient selection criteria for proton therapy, leading to low referral rates [11].

8.3. Lack of Prospective Randomized Data

The most significant limitation in the evidence base for proton therapy in gynecological malignancies is the paucity of prospective randomized trials comparing proton therapy with modern photon techniques [11]. The existing literature consists primarily of dosimetric planning studies, small single-institution retrospective series, and prospective registries without randomized comparisons. While these studies provide valuable in-

sights into dosimetric advantages and feasibility, they cannot definitively establish clinical superiority [11].

Randomized trials of radiation therapy modalities face several challenges [73]. The substantial differences in infrastructure and workflow between proton and photon therapy make blinding impossible, potentially introducing bias in outcome assessment [73]. Patient and physician preferences may lead to selection bias if randomization is refused. The need for patients to travel to proton therapy centers creates logistical barriers to trial participation [73]. Additionally, the relatively long follow-up required to assess late toxicity and survival outcomes necessitates sustained funding and institutional commitment [73].

Despite these challenges, randomized trials are essential to definitively establish the role of proton therapy in gynecological malignancies [74]. Such trials should employ patient-reported outcomes as primary or co-primary endpoints, as these may be more sensitive to differences in treatment modality than clinician-graded toxicity scales [74]. Quality of life assessments, functional outcomes, and economic analyses should be integrated into trial designs [74]. Pragmatic trial designs that reflect real-world practice patterns may enhance feasibility and generalizability [74].

8.4. Technical Challenges

8.4.1. Range Uncertainty

Proton range uncertainty is a fundamental challenge in proton therapy, arising from multiple sources, including CT Hounsfield unit to stop power conversion errors, patient positioning uncertainties, organ motion, and anatomical changes during treatment [75]. For gynecological malignancies, where targets are surrounded by tissues of varying density (bone, muscle, fat, air in bowel and bladder), range uncertainties can significantly impact dose distributions [75].

Current clinical practice typically employs range uncertainty margins of 3.5% of the beam range plus 1–3 mm, though the optimal margin remains debated [76]. Robust optimization techniques explicitly account for range uncertainties during treatment planning but cannot eliminate the underlying physical uncertainties [76]. Advances in imaging, including dual-energy CT and proton radiography, may reduce range uncertainties, but these technologies are not yet widely available [76].

8.4.2. Organ Motion and Anatomical Changes

Bladder and rectal filling variations, bowel motion, tumor response, and weight changes during treatment can significantly alter anatomy in the pelvis [77]. For proton therapy, these changes can shift the Bragg peak position, potentially leading to underdosage of the target or overdosage of OARs [77]. Daily image guidance and adaptive replanning strategies are essential to manage these challenges, but add complexity and resource requirements to treatment delivery [77].

The development of online adaptive proton therapy, where the treatment plan is modified immediately before each fraction based on the day's anatomy, represents a potential solution but requires substantial advances in imaging, treatment planning speed, and quality assurance workflows [78]. Such capabilities are beginning to emerge for photon therapy with MR-linac systems, but remain largely aspirational for proton therapy [78].

8.4.3. Interplay Effects

For pencil-beam scanning proton therapy, the interaction between beam scanning motion and organ motion can create interplay effects that cause dose heterogeneities [79]. While these effects are generally less pronounced for pelvic treatments than for thoracic

treatments (where respiratory motion is more significant), they remain a consideration, particularly for targets near mobile structures like bowel [79]. Mitigation strategies include rescanning (delivering the same spot pattern multiple times), breath-hold techniques, and motion management, but these approaches add complexity to treatment delivery [79].

8.5. Quality Assurance and Credentialing

The technical complexity of proton therapy necessitates rigorous quality assurance programs and specialized training for radiation oncologists, medical physicists, dosimetrists, and therapists. The relative novelty of proton therapy means that many practitioners have limited experience with the modality, and standardized credentialing processes are still evolving [80].

For clinical trials of proton therapy, ensuring consistent treatment planning and delivery across multiple institutions is challenging. Benchmark cases, central review of treatment plans, and site qualification procedures are essential but resource-intensive [81]. The development of consensus guidelines for proton therapy in gynecological malignancies would facilitate standardization and quality assurance.

9. Future Directions and Ongoing Clinical Trials

9.1. Prospective Clinical Trials

Several prospective trials are underway or planned to evaluate proton therapy for gynecological malignancies, addressing the critical evidence gap in randomized comparative data.

The PROTECT trial (Prospective Phase-II-Trial Evaluating Adaptive Proton Therapy for Cervical Cancer to Reduce the Impact on Morbidity and the Immune System) is a non-randomized prospective multicenter phase II study including 30 women with locally advanced cervical cancer [35]. The trial evaluates whether IMPT enables significant dose reduction to organs at risk compared to IMRT/VMAT. Primary endpoints include pelvic bone mean dose and mean bowel V15Gy, with secondary endpoints encompassing dosimetric parameters, oncological outcomes, health-related quality of life, immune response, safety, and tolerability [35]. Critically, future trials beyond PROTECT and APROVE must incorporate locoregional control, progression-free survival, and overall survival as co-primary or key secondary endpoints, in addition to toxicity and quality of life metrics. Without oncologic efficacy data, the role of proton therapy in gynecological malignancies cannot be definitively established, regardless of the magnitude of dosimetric or toxicity improvements,

The APROVE trial (A Prospective Phase-II-Study Evaluating Postoperative Radiotherapy of Cervical and Endometrial Cancer Patients Using Protons) is a prospective single-center one-arm phase II study planning to enroll 25 patients over two years [46]. The study includes patients with cervical or endometrial cancer after surgical resection who have an indication for postoperative pelvic radiotherapy. The primary endpoint is the absence of any CTCAE Grade 3 or 4 toxicity, with secondary endpoints including clinical symptoms and toxicity, quality of life (EORTC-QLQ30/-EN24/-CX24), and progression-free survival [46].

Additional trials are needed to address specific clinical questions, including

- Randomized comparison of IMPT versus IMRT for definitive chemoradiation in cervical cancer;
- Evaluation of proton therapy for extended-field radiation in node-positive disease;
- Assessment of proton therapy for reirradiation of recurrent gynecological malignancies;

- Integration of proton therapy with immunotherapy and targeted agents;
- Cost-effectiveness analyses comparing proton therapy with modern photon techniques.

9.2. Technological Advances

9.2.1. FLASH Proton Therapy

FLASH radiation therapy—delivery of ultra-high dose rates (>40 Gy/second)—has emerged as a promising approach to reduce normal tissue toxicity while maintaining tumor control [82]. Preclinical studies have demonstrated a "FLASH effect" where normal tissues exhibit reduced toxicity when irradiated at ultra-high dose rates, while tumor response is preserved. Proton therapy is particularly well-suited for FLASH delivery due to the high dose rates achievable with pencil-beam scanning systems [82].

For gynecological malignancies, FLASH proton therapy could potentially further reduce gastrointestinal, genitourinary, and hematologic toxicities beyond what is achievable with conventional dose rate proton therapy [82]. However, substantial technical challenges remain, including beam delivery system modifications, dosimetry at ultra-high dose rates, and treatment planning optimization [82]. Clinical trials of FLASH proton therapy are in early phases, and applications to gynecological malignancies remain investigational [82].

9.2.2. Proton Arc Therapy

Proton arc therapy, analogous to photon VMAT, involves continuous beam delivery while the gantry rotates around the patient [83]. This approach may offer improved distributions and reduced treatment times compared to static-field IMPT. For gynecological malignancies, proton arc therapy could potentially provide even better OAR sparing by optimizing beam angles throughout the 360-degree arc [83].

Technical challenges for proton arc therapy include energy layer switching during gantry rotation, real-time spot position adjustment, and quality assurance of continuously varying beam parameters. Several proton therapy centers are developing proton arc capabilities, and clinical implementation is anticipated in the coming years [83].

9.2.3. Artificial Intelligence and Machine Learning

Artificial intelligence (AI) and machine learning (ML) technologies are being applied to multiple aspects of proton therapy, including automated treatment planning, outcome prediction, adaptive replanning, and quality assurance [84]. For gynecological malignancies, AI/ML could potentially

- Automate target and OAR segmentation on CT and MRI;
- Generate optimized treatment plans that balance target coverage and OAR sparing;
- Predict which patients are most likely to benefit from proton therapy based on anatomical and clinical features;
- Identify anatomical changes during treatment that warrant adaptive replanning;
- Predict toxicity risk, based on dose distributions and patient factors.

Several research groups are developing AI/ML tools for proton therapy, though clinical validation and regulatory approval remain ongoing [84]. The integration of these technologies into clinical workflows could enhance efficiency, consistency, and outcomes. The convergence of these future frontiers, including AI-driven optimization, FLASH dose rates, and advanced biomarker integration, is illustrated in Figure 7.

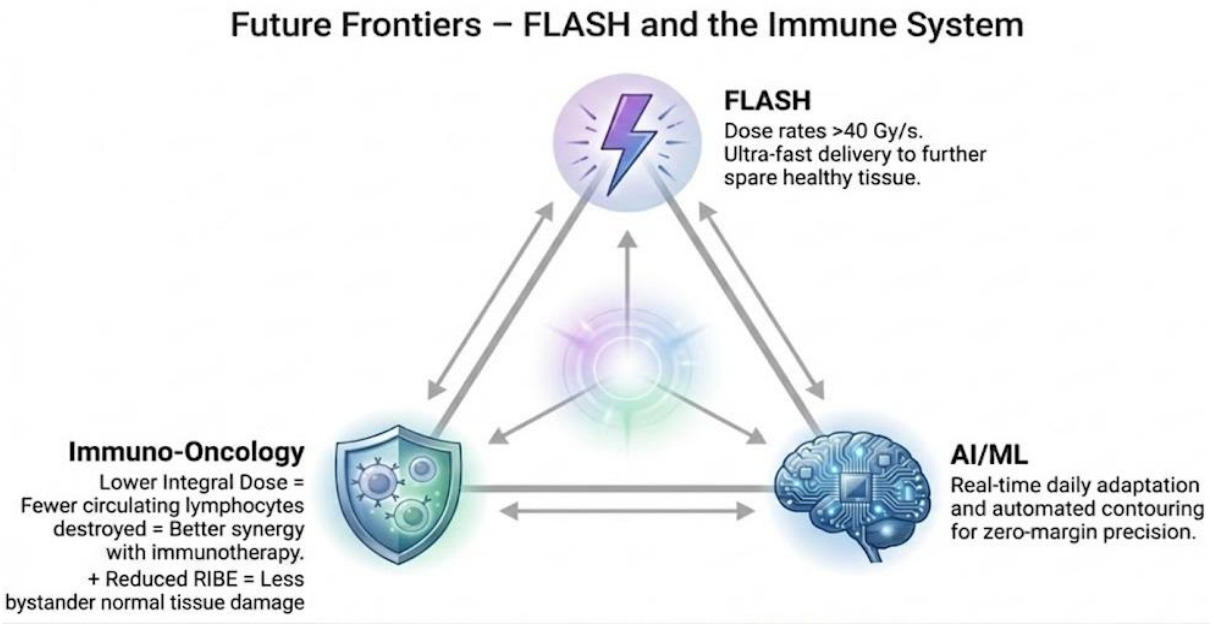

Figure 7. Future frontiers in proton therapy for gynecological malignancies. This conceptual summary illustrates the integration of emerging technologies designed to further enhance the therapeutic ratio of proton beam therapy. FLASH Therapy: Delivery of ultra-high dose rates (>40 Gy/s) to exploit the "FLASH effect," potentially increasing the sparing of healthy pelvic tissues while maintaining robust tumor control. AI/ML: Real-time daily adaptation and automated contouring for zero-margin precision, enabling personalized treatment optimization. Immuno-Oncology: Lower integral dose results in fewer circulating lymphocytes destroyed, producing better synergy with immunotherapy. Additionally, reduced radiation-induced bystander effects (RIBE), whereby non-irradiated cells exhibit DNA damage or apoptosis through paracrine signaling from irradiated neighbors, may further limit normal tissue injury and potentially augment abscopal anti-tumor immune responses. The interplay between FLASH ultra-high dose rates and RIBE signaling pathways represents an emerging area of investigation. The three nodes are mutually reinforcing: AI-driven precision reduces unnecessary dose, FLASH spares normal tissue at ultra-high rates, and together these effects preserve immune competence and enhance immunotherapy synergy. Created in BioRender. Bakshi H. (2026) https://BioRender.com/Basic.

9.3. Biomarker Development

The development of predictive biomarkers to identify patients most likely to benefit from proton therapy would facilitate personalized treatment selection and improve cost-effectiveness. Potential biomarkers include

Anatomical biomarkers: Patients with anatomical features that result in high OAR doses with photon therapy (e.g., large-bowel volumes in the pelvis, extensive bone marrow in treatment fields) may derive greater benefit from proton therapy. Automated analysis of planning CT scans could identify such patients [85].

Genetic biomarkers: Patients with genetic variants associated with increased radiation sensitivity or impaired DNA repair may be at higher risk for toxicity and could preferentially benefit from the reduced integral dose of proton therapy. Germline genetic testing for radiation sensitivity variants is an area of active research [86].

Tumor biomarkers: Tumors with specific molecular features (e.g., hypoxia, immune infiltration) may respond differently to proton versus photon therapy due to differences in LET and dose distribution. Identification of such features could guide treatment selection [87].

Functional biomarkers**:** Baseline organ function (e.g., bone marrow reserve, bowel function, bladder capacity) may predict tolerance of radiation therapy and benefit from OAR sparing with proton therapy [88].

The integration of multi-omic data (genomics, radiomics, dosimetrics) with machine learning approaches may enable the development of comprehensive prediction models for treatment selection.

9.4. Consensus Guidelines and Patient Selection Criteria

The development of evidence-based consensus guidelines for proton therapy in gynecological malignancies is essential to standardize practice and facilitate appropriate patient selection. Such guidelines should address

- Clinical scenarios where proton therapy is recommended, optional, or not indicated;
- Dosimetric criteria for patient selection (e.g., minimum OAR dose reduction thresholds);
- Technical requirements for treatment planning and delivery;
- Quality assurance standards;
- Outcome reporting standards for clinical trials and registries.

Professional societies, including the American Society for Radiation Oncology (ASTRO), the European Society for Radiotherapy and Oncology (ESTRO), and the Particle Therapy Co-Operative Group (PTCOG), are developing model policies and guidelines for proton therapy [89,90]. Specific guidelines for gynecological malignancies should be developed through multidisciplinary consensus processes involving radiation oncologists, gynecologic oncologists, medical physicists, and patient advocates [89].

9.5. Global Access and Health Equity

Addressing the substantial disparities in access to proton therapy is essential for realizing the potential benefits of this technology for all patients who might benefit. Strategies to improve access include

Technology development: Compact, lower-cost proton therapy systems are under development, which could reduce capital costs and enable deployment in more settings. Single-room systems and superconducting cyclotron technologies may reduce costs by 50% or more compared to conventional multi-room centers [70].

Reimbursement reform: Evidence-based reimbursement policies that appropriately value the potential benefits of proton therapy while ensuring cost-effectiveness could improve access. Value-based payment models that reward outcomes rather than simply procedure volume may be appropriate [91].

Telemedicine and remote consultation: Telemedicine platforms could facilitate remote consultation with proton therapy specialists, helping community oncologists identify appropriate candidates for referral and coordinate care [92].

International collaboration: Partnerships between high-income and low- and middle-income countries could facilitate technology transfer, training, and research collaboration to expand global access to proton therapy [93].

Clinical trial participation: Expanding clinical trial networks to include more diverse patient populations and geographic regions could improve both evidence generation and access to proton therapy [94–98].

10. Conclusions

Proton beam therapy offers well-documented dosimetric advantages in gynecological malignancies, particularly in reducing dose to small bowel, pelvic bone marrow, bladder, and rectum. These dosimetric benefits are consistent across planning studies. Early

clinical data—most notably the Anderson et al. prospective registry study and the Wark et al. matched-cohort study—provide preliminary evidence that these advantages may translate into reduced acute gastrointestinal and hematologic toxicity. However, it must be explicitly stated that no randomized controlled trial has confirmed clinical superiority of proton over modern photon therapy in this disease site, and no survival or locoregional control benefit has been established. All clinical benefit claims remain preliminary and are subject to prospective validation through ongoing and future trials [5,31].

However, the evidence base remains limited by the predominance of planning studies and small retrospective cohorts, with a critical lack of prospective randomized trials comparing proton therapy with modern photon techniques [73]. The existing data, while promising, are insufficient to definitively establish clinical superiority or to justify routine use of proton therapy for all gynecological cancer patients [74]. Ongoing prospective trials, including the PROTECT and APROVE studies, will provide essential data on clinical outcomes, toxicity, and quality of life, helping to define the appropriate role of proton therapy in clinical practice [35,46,74].

These early findings warrant cautious optimism rather than definitive conclusions. The prospective registry study (Anderson et al., $n = 67$) is the strongest available clinical evidence and shows promising patient-reported GI symptom differences, but was not designed nor powered as a superiority trial [5]. The matched-cohort hematotoxicity data (Wark et al.) are subject to the confounding factors outlined in Section 3.4. Completion of the PROTECT and APROVE trials, and initiation of appropriately powered randomized trials with oncologic co-endpoints, are required before proton therapy can be recommended for routine use in gynecological malignancies beyond carefully selected cases [31].

Special clinical scenarios, including postoperative pelvic irradiation, extended-field nodal treatment, and reirradiation for recurrent disease, represent particularly promising applications where the dosimetric advantages of proton therapy may be most pronounced [44]. The integration of proton therapy with systemic therapies, including chemotherapy, targeted agents, and immunotherapy, warrants further investigation, with particular attention to the potential for reduced bone marrow exposure to preserve immune function [52]. Adaptive treatment strategies incorporating MRI-guided target tailoring and robust optimization techniques may further enhance the therapeutic ratio of proton therapy [52].

Current limitations, including high costs, limited accessibility, technical challenges related to range uncertainties and organ motion, and insufficient long-term outcome data, must be addressed to realize the full potential of proton therapy for gynecological malignancies [17]. The development of more compact and cost-effective proton therapy systems, advances in imaging and adaptive planning technologies, and evidence-based reimbursement policies could improve access and cost-effectiveness [14]. International collaboration and clinical trial networks are essential to generate the high-quality evidence needed to guide clinical decision-making and health policy [14].

Future directions include prospective randomized trials with patient-reported outcomes as primary endpoints, technological advances including FLASH proton therapy and proton arc therapy, development of predictive biomarkers for patient selection, and creation of evidence-based consensus guidelines [82]. The integration of artificial intelligence and machine learning into proton therapy workflows may enhance treatment planning, outcome prediction, and quality assurance [82]. Addressing global disparities in access to proton therapy is essential to ensure that the benefits of this technology are available to all patients who might benefit, regardless of geographic location or socioeconomic status [71].

In conclusion, proton beam therapy holds significant promise for improving outcomes and reducing toxicity in gynecological malignancies. The physical advantages are clear, and early clinical data are encouraging. However, definitive establishment of clini-

cal benefit requires completion of ongoing prospective trials and initiation of additional randomized studies. As the evidence base matures and technology advances, proton therapy is likely to play an increasingly important role in the multidisciplinary management of gynecological cancers, particularly for carefully selected patients where the dosimetric advantages are most pronounced and the potential for toxicity reduction is greatest. Continued research, technological innovation, and collaborative efforts to improve access will be essential to translate the promise of proton therapy into improved outcomes for women with gynecological malignancies.

Author Contributions: Conceptualization, H.A.B.; methodology, H.A.B., L.C., and L.W.; software, H.A.B.; validation, L.C., L.W., and H.A.B.; formal analysis, L.C.; investigation, L.C.; resources, L.W.; data curation, H.A.B.; writing—original draft preparation, L.C. and L.W.; writing—review and editing, H.A.B.; visualization, L.C.; supervision, H.A.B.; project administration, H.A.B.; funding acquisition, H.A.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Acknowledgments: The authors would like to thank the Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, for providing the facilities, core, and resources used in this study.

Conflicts of Interest: The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of this manuscript; or in the decision to publish the results.

References

1. Cun, H.T.; Bedell, S.M.; Kimball, J.; Gaffney, D.K.; Hasan, Y. Radiation therapy for the gynecologic oncologist. *Gynecol. Oncol.* **2026**, *204*, 79–90. https://doi.org/10.1016/j.ygyno.2025.10.030. PMID: 41289794.
2. Jain, S.; Kumar, P.; Kumar, P.; Nigam, J.; Silambarasan, N.S.; Sachan, R. Intensity-modulated Radiotherapy Versus Volumetric Modulated Arc Therapy in Head and Neck Cancers: A Comparative Analysis of Compliance, Toxicities and Dosimetric Parameters. *Cureus* **2025**, *17*, e86143. https://doi.org/10.7759/cureus.86143. PMID: 40672034; PMCID: PMC12265974.
3. Yoshimura, T.; Yamada, R.; Kinoshita, R.; Matsuura, T.; Kanehira, T.; Tamura, H.; Nishioka, K.; Yasuda, K.; Taguchi, H.; Katoh, N.; et al. Probability of normal tissue complications for hematologic and gastrointestinal toxicity in postoperative whole pelvic radiotherapy for gynecologic malignancies using intensity-modulated proton therapy with robust optimization. *J. Radiat. Res.* **2024**, *65*, 369–378. https://doi.org/10.1093/jrr/rrae008. PMID: 38499489; PMCID: PMC11115445.
4. Georg D.; Kirisits C.; Hillbrand M.; Dimopoulos J.; Pötter R. Image-Guided Radiotherapy for Cervix Cancer: High-Tech External Beam Therapy Versus High-Tech Brachytherapy. *Int. J. Radiat. Oncol. Biol. Phys.* **2008**, *71*, 1272–1278. https://doi.org/10.1016/J.IJROBP.2008.03.032.
5. Anderson, J.D.; Voss, M.M.; Laughlin, B.S.; Garda, A.E.; Aziz, K.; Mullikin, T.C.; Haddock, M.G.; Petersen, I.A.; DeWees, T.A.; Vora, S.A. Outcomes of Proton Beam Therapy Compared With Intensity-Modulated Radiation Therapy for Uterine Cancer. *Int. J. Part. Ther.* **2022**, *9*, 10–17. https://doi.org/10.14338/IJPT-22-00020.1. PMID: 36721479; PMCID: PMC9875825.
6. Stovall, M. Fetal dose from radiotherapy with photon beams: Report of AAPM Radiation Therapy Committee Task Group No. 36. *Med. Phys.* **1995**, *22*, 63–82. https://doi.org/10.1118/1.597525.
7. De Santis, M.; Di Gianantonio, E.; Straface, G.; Cavaliere, A.F.; Caruso, A.; Schiavon, F.; Berletti, R.; Clementi, M. Ionizing radiations in pregnancy and teratogenesis: A review of literature. *Reprod. Toxicol.* **2005**, *20*, 323–329. https://doi.org/10.1016/j.reprotox.2005.04.004.

8. Lin, D.; Lehrer, E.J.; Rosenberg, J.; Trifiletti, D.M.; Zaorsky, N.G. Toxicity after radiotherapy in patients with historically accepted contraindications to treatment (CONTRAD): An international systematic review and meta-analysis. *Radiother. Oncol.* **2019**, *135*, 147–152. https://doi.org/10.1016/j.radonc.2019.03.006.
9. Kavanagh, B.D.; Pan, C.C.; Dawson, L.A.; Das, S.K.; Li, X.A.; Ten Haken, R.K.; Miften, M. Radiation dose-volume effects in the stomach and small bowel. *Int. J. Radiat. Oncol. Biol. Phys.* **2010**, *76*, S101–S107. https://doi.org/10.1016/j.ijrobp.2009.05.071.
10. Isohashi, F.; Yoshioka, Y.; Mabuchi, S.; Konishi, K.; Koizumi, M.; Takahashi, Y.; Ogata, T.; Maruoka, S.; Kimura, T.; Ogawa, K. Dose-volume histogram predictors of chronic gastrointestinal complications after radical hysterectomy and postoperative concurrent nedaplatin-based chemoradiation therapy for early-stage cervical cancer. *Int. J. Rad.* **2013**, *85*, 728–734. https://doi.org/10.1016/j.ijrobp.2012.05.021.
11. Capozzi, V.A.; Martignon, G.; Scarpelli, E.; De Finis, A.; Restaino, S.; Vizzielli, G.; Berretta, R. Proton Beam Therapy in Gynecological Cancers: A Systematic Review of Indications, Complications, and Limitations. *Medicina* **2026**, *62*, 334. https://doi.org/10.3390/medicina62020334. PMID: 41752732; PMCID: PMC12941855.
12. Taunk, N. The role of proton therapy in gynecological radiation oncology. *Int. J. Gynecol. Cancer* **2022**, *32*, 414–420. https://doi.org/10.1136/ijgc-2021-002459. PMID: 35256431.
13. Byun, H.K.; Han, M.C.; Yang, K.; Kim, J.S.; Yoo, G.S.; Koom, W.S.; Kim, Y.B. Physical and Biological Characteristics of Particle Therapy for Oncologists. *Cancer Res. Treat.* **2021**, *53*, 611–620. https://doi.org/10.4143/crt.2021.066. PMID: 34139805; PMCID: PMC8291193.
14. Mohan, R.; Grosshans, D. Proton therapy—Present and future. *Adv. Drug Deliv. Rev.* **2017**, *109*, 26–44. https://doi.org/10.1016/j.addr.2016.11.006. PMID: 27919760; PMCID: PMC5303653.
15. Chang, J.Y.; Jabbour, S.K.; De Ruysscher, D.; Schild, S.E.; Simone, C.B., 2nd; Rengan, R.; Feigenberg, S.; Khan, A.J.; Choi, N.C.; Bradley, J.D.; et al. Consensus Statement on Proton Therapy in Early-Stage and Locally Advanced Non-Small Cell Lung Cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **2016**, *95*, 505–516. https://doi.org/10.1016/j.ijrobp.2016.01.036. PMID: 27084663; PMCID: PMC10868643.
16. Bayasgalan, U.; Moon, S.H.; Kim, T.H.; Kim, T.Y.; Lee, S.H.; Suh, Y.G. Dosimetric Comparisons between Proton Beam Therapy and Modern Photon Radiation Techniques for Stage I Non-Small Cell Lung Cancer According to Tumor Location. *Cancers* **2021**, *13*, 6356. https://doi.org/10.3390/cancers13246356. PMID: 34944976; PMCID: PMC8699272.
17. Mohan, R. A Review of Proton Therapy—Current Status and Future Directions. *Precis. Radiat. Oncol.* **2022**, *6*, 164–176. https://doi.org/10.1002/pro6.1149. PMID: 36160180; PMCID: PMC9499036.
18. Moreno, A.C.; Frank, S.J.; Garden, A.S.; Rosenthal, D.I.; Fuller, C.D.; Gunn, G.B.; Reddy, J.P.; Morrison, W.H.; Williamson, T.D.; Holliday, E.B.; et al. Intensity modulated proton therapy (IMPT)—The future of IMRT for head and neck cancer. *Oral Oncol.* **2019**, *88*, 66–74. https://doi.org/10.1016/j.oraloncology.2018.11.015. PMID: 30616799; PMCID: PMC6615027.
19. Paganetti, H.; Blakely, E.; Carabe-Fernandez, A.; Carlson, D.J.; Das, I.J.; Dong, L.; Grosshans, D.; Held, K.D.; Mohan, R.; Moiseenko, V.; et al. Report of the AAPM TG-256 on the relative biological effectiveness of proton beams in radiation therapy. *Med. Phys.* **2019**, *46*, e53–e78. https://doi.org/10.1002/mp.13390.
20. Deng, W.; Yang, Y.; Liu, C.; Bues, M.; Mohan, R.; Wong, W.W.; Foote, R.H.; Patel, S.H.; Liu, W. A Critical Review of LET-Based Intensity-Modulated Proton Therapy Plan Evaluation and Optimization for Head and Neck Cancer Management. *Int. J. Part. Ther.* **2021**, *8*, 36–49. https://doi.org/10.14338/IJPT-20-00049.1. PMID: 34285934; PMCID: PMC8270082.
21. Reiners, K.; Artz, M.; Bryant, C.M.; Dagan, R.; Grewal, H.S.; Johnson, P.B.; Li, Z.; Park, J.; Vieceli, M.; Zhang, Y. RBE-Guided Treatment Planning, LET Optimization, and Implications of Proton Arc Therapy for the Sparing of Nervous Tissue in Head and Neck Proton Therapy. *Cancers* **2025**, *17*, 3724. https://doi.org/10.3390/cancers17233724. PMID: 41374925; PMCID: PMC12691369.
22. Lomax, A.J.; Boehringer, T.; Coray, A.; Egger, E.; Goitein, G.; Grossmann, M.; Juelke, P.; Lin, S.; Pedroni, E.; Rohrer, B.; et al. Intensity modulated proton therapy: A clinical example. *Med. Phys.* **2001**, *28*, 317–324. https://doi.org/10.1118/1.1350587. PMID: 11318312.
23. Marnitz, S.; Wlodarczyk, W.; Neumann, O.; Koehler, C.; Weihrauch, M.; Budach, V.; Cozzi, L. Which technique for radiation is most beneficial for patients with locally advanced cervical cancer? Intensity modulated proton therapy versus intensity modulated photon treatment, helical tomotherapy and volumetric arc therapy for primary radiation—An intraindividual comparison. *Radiat. Oncol.* **2015**, *10*, 91. https://doi.org/10.1186/s13014-015-0402-z. PMID: 25896675; PMCID: PMC4404108.
24. Ger, R.B.; Lentz, J.M.; Niedzielski, J.S.; Vora, S.A.; Bues, M.; Hernandez Morales, D.; Anderson, J.D.; Kutyreff, C.J.; Schulz, C.A.; Lara, P.R.; et al. Dosimetric Advantage of Scanning Beam Proton Therapy in Gynecologic Patients Receiving Adjuvant Radiotherapy. *Cancers* **2025**, *17*, 2010. https://doi.org/10.3390/cancers17122010. PMID: 40563662; PMCID: PMC12190590.

25. Xu, M.J.; Maity, A.; Vogel, J.; Kirk, M.; Zhai, H.; Both, S.; Lin, L.L. Proton Therapy Reduces Normal Tissue Dose in Extended-Field Pelvic Radiation for Endometrial Cancer. *Int. J. Part. Ther.* **2018**, *4*, 1–11. https://doi.org/10.14338/IJPT-17-00027.1. PMID: 31773009; PMCID: PMC6871568.
26. Parker, R.G.; Greenberg, P. Treatment planning for particle radiation therapy. *Front. Radiat. Ther. Oncol.* **1987**, *21*, 84–93. https://doi.org/10.1159/000413241. PMID: 3032751.
27. de Boer, P.; van de Schoot, A.J.A.J.; Westerveld, H.; Smit, M.; Buist, M.R.; Bel, A.; Rasch, C.R.N.; Stalpers, L.JA. Target tailoring and proton beam therapy to reduce small bowel dose in cervical cancer radiotherapy: A comparison of benefits. *Strahlenther. Onkol.* **2018**, *194*, 255–263. https://doi.org/10.1007/s00066-017-1224-8. PMID: 29101415; PMCID: PMC5847034.
28. Hashimoto, S.; Shibamoto, Y.; Iwata, H.; Ogino, H.; Shibata, H.; Toshito, T.; Sugie, C.; Mizoe, J.E. Whole-pelvic radiotherapy with spot-scanning proton beams for uterine cervical cancer: A planning study. *J. Radiat. Res.* **2016**, *57*, 524–532. https://doi.org/10.1093/jrr/rrw052. PMID: 27380800; PMCID: PMC5045079.
29. Shang, H.; Pu, Y.; Wang, W.; Dai, Z.; Jin, F. Evaluation of plan quality and robustness of IMPT and helical IMRT for cervical cancer. *Radiat. Oncol.* **2020**, *15*, 34. https://doi.org/10.1186/s13014-020-1483-x. PMID: 32054496; PMCID: PMC7020599.
30. Sharma, M.K.; Hug, E.B.; Bhushan, M.; Mah, D.; Maes, D.; Gairola, M.; Sharma, S.K.; Yadav, G.; Pal, M.; Chauhan, D.; et al. Dosimetric Comparison of Pencil-Beam Scanning and Photon-Based Radiation Therapy as a Boost in Carcinoma of Cervix. *Int. J. Part. Ther.* **2017**, *4*, 1–10. https://doi.org/10.14338/IJPT-17-00009. PMID: 31773003; PMCID: PMC6871551.
31. Wark, A.; Gupta, A.; Meixner, E.; König, L.; Hörner-Rieber, J.; Forster, T.; Lang, K.; Ellerbrock, M.; Herfarth, K.; Debus, J.; et al. Bone Marrow Sparing by Intensity Modulated Proton Beam Therapy in Postoperative Irradiation of Gynecologic Malignancies. *Technol. Cancer Res. Treat.* **2024**, *22*, 15330338241252622. https://doi.org/10.1177/15330338241252622. PMID: 38845139; PMCID: PMC11159539.
32. Holschneider CH, Petereit DG, Chu C, Hsu IC, Ioffe YJ, Klopp AH, Pothuri B, Chen LM, Yashar C. Brachytherapy: A critical component of primary radiation therapy for cervical cancer: From the Society of Gynecologic Oncology (SGO) and the American Brachytherapy Society (ABS). *Brachytherapy* **2019**, *18*, 123–132. https://doi.org/10.1016/j.brachy.2018.11.009. PMID: 30665713.
33. Song, W.Y.; Huh, S.N.; Liang, Y.; White, G.; Nichols, R.C.; Watkins, W.T.; Mundt, A.J.; Mell, L.K. Dosimetric comparison study between intensity modulated radiation therapy and three-dimensional conformal proton therapy for pelvic bone marrow sparing in the treatment of cervical cancer. *J. Appl. Clin. Med. Phys.* **2010**, *11*, 3255. https://doi.org/10.1120/jacmp.v11i4.3255. PMID: 21081882; PMCID: PMC5720421.
34. Lin, L.L.; Kirk, M.; Scholey, J.; Taku, N.; Kiely, J.B.; White, B.; Both, S. Initial Report of Pencil Beam Scanning Proton Therapy for Posthysterectomy Patients With Gynecologic Cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **2016**, *95*, 181–189. https://doi.org/10.1016/j.ijrobp.2015.07.2205. PMID: 26372435.
35. Corbeau, A.; Nout, R.A.; Mens, J.W.M.; Horeweg, N.; Godart, J.; Kerkhof, E.M.; Kuipers, S.C.; van Poelgeest, M.I.E.; Kroep, J.R.; Boere, I.A.; et al. PROTECT: Prospective Phase-II-Trial Evaluating Adaptive Proton Therapy for Cervical Cancer to Reduce the Impact on Morbidity and the Immune System. *Cancers* **2021**, *13*, 5179. https://doi.org/10.3390/cancers13205179. PMID: 34680328; PMCID: PMC8533850.
36. Blanchard, P.; Wong, A.J.; Gunn, G.B.; Garden, A.S.; Mohamed, A.S.R.; Rosenthal, D.I.; Crutison, J.; Wu, R.; Zhang, X.; Zhu, X.R.; et al. Toward a model-based patient selection strategy for proton therapy: External validation of photon-derived normal tissue complication probability models in a head and neck proton therapy cohort. *Radiother. Oncol.* **2016**, *121*, 381–386. https://doi.org/10.1016/j.radonc.2016.08.022. PMID: 27641784; PMCID: PMC5474306.
37. Massobrio, R.; Bianco, L.; Campigotto, B.; Attianese, D.; Maisto, E.; Pascotto, M.; Ruo Redda, M.G.; Ferrero, A. New Frontiers in Locally Advanced Cervical Cancer Treatment. *J. Clin. Med.* **2024**, *13*, 4458. https://doi.org/10.3390/jcm13154458. PMID: 39124724; PMCID: PMC11312973.
38. Kagei, K.; Tokuuye, K.; Okumura, T.; Ohara, K.; Shioyama, Y.; Sugahara, S.; Akine, Y. Long-term results of proton beam therapy for carcinoma of the uterine cervix. *Int. J. Radiat. Oncol. Biol. Phys.* **2003**, *55*, 1265–1271. https://doi.org/10.1016/s0360-3016(02)04075-0. PMID: 12654436.
39. Latif, N.A.; Haggerty, A.; Jean, S.; Lin, L.; Ko, E. Adjuvant therapy in early-stage endometrial cancer: A systematic review of the evidence, guidelines, and clinical practice in the U.S. *Oncologist* **2014**, *19*, 645–653. https://doi.org/10.1634/theoncologist.2013-0475. PMID: 24821823; PMCID: PMC4041674.
40. Fields, E.C.; McGuire, W.P.; Lin, L.; Temkin, S.M. Radiation Treatment in Women with Ovarian Cancer: Past, Present, and Future. *Front. Oncol.* **2017**, *7*, 177. https://doi.org/10.3389/fonc.2017.00177. PMID: 28871275; PMCID: PMC5566993.

41. Macchia, G.; Titone, F.; Restaino, S.; Arcieri, M.; Pellecchia, G.; Andreetta, C.; Driul, L.; Vizzielli, G.; Pezzulla, D. Is It Time to Reassess the Role of Radiotherapy Treatment in Ovarian Cancer? *Healthcare* **2023**, *11*, 2413. https://doi.org/10.3390/healthcare11172413. PMID: 37685447; PMCID: PMC10486999.
42. Endo, Y.; Takagawa, Y.; Yoshimoto, Y.; Machida, M.; Dai, Y.; Azami, Y.; Seto, I.; Takayama, K.; Suzuki, M.; Nakasato, T.; et al. Proton beam therapy achieves excellent local control for recurrent epithelial ovarian cancer: A single-center retrospective study. *J. Ovarian Res.* **2025**, *18*, 110. https://doi.org/10.1186/s13048-025-01695-2. PMID: 40426272; PMCID: PMC12108022.
43. Simone CB2nd Plastaras, J.P.; Jabbour, S.K.; Lee, A.; Lee, N.Y.; Choi, J.I.; Frank, S.J.; Chang, J.Y.; Bradley, J. Proton Reirradiation: Expert Recommendations for Reducing Toxicities and Offering New Chances of Cure in Patients With Challenging Recurrence Malignancies. *Semin. Radiat. Oncol.* **2020**, *30*, 253–261. https://doi.org/10.1016/j.semradonc.2020.02.007. PMID: 32503791; PMCID: PMC10870390.
44. Jhingran, A. Updates in the treatment of vaginal cancer. *Int. J. Gynecol. Cancer* **2022**, *32*, 344–351. https://doi.org/10.1136/ijgc-2021-002517. PMID: 35256422; PMCID: PMC8921584.
45. Frank, S.J.; Jhingran, A.; Levenback, C.; Eifel, P.J. Definitive radiation therapy for squamous cell carcinoma of the vagina. *Int. J. Radiat. Oncol. Biol. Phys.* **2005**, *62*, 138–147. https://doi.org/10.1016/j.ijrobp.2004.09.032. PMID: 15850914.
46. Arians, N.; Lindel, K.; Krisam, J.; Herfarth, K.; Krug, D.; Akbaba, S.; Oelmann-Avendano, J.; Debus, J. Prospective phase-II-study evaluating postoperative radiotherapy of cervical and endometrial cancer patients using protons—The APROVE-trial. *Radiat. Oncol.* **2017**, *12*, 188. https://doi.org/10.1186/s13014-017-0926-5. PMID: 29179751; PMCID: PMC5704365.
47. DeCesaris, C.; Bedell, S.; Kelley, K.; Gaffney, D.; Suneja, G.; Burt, L.; Jarboe, E.; Brower, J. Use of Radiation Therapy in the Management of Vulvar Cancers-Identification and Management of Acute and Late Toxicities. *Pract. Radiat. Oncol.* **2025**, *15*, e57–e62. https://doi.org/10.1016/j.prro.2024.08.006. PMID: 39303777.
48. Del Sorbo, V.; Pentangelo, P.; Verrazzo, P.; Papa, R.; Alfano, C. Reconstructive Surgery of the Female Genital, Urethral, and Anal Tract: A Multidisciplinary Review and Future Perspectives. *J. Pers. Med.* **2025**, *15*, 613. https://doi.org/10.3390/jpm15120613. PMID: 41440976; PMCID: PMC12734212.
49. Li, Y.R.; Kirk, M.; Lin, L. Proton Therapy for Vaginal Reirradiation. *Int. J. Part. Ther.* **2016**, *3*, 320–326. https://doi.org/10.14338/IJPT-16-00013.1. PMID: 28989947; PMCID: PMC5627360.
50. Zhou, P.; Du, Y.; Zhang, Y.; Zhu, M.; Li, T.; Tian, W.; Wu, T.; Xiao, Z. Efficacy and Safety in Proton Therapy and Photon Therapy for Patients With Esophageal Cancer: A Meta-Analysis. *JAMA Netw. Open* **2023**, *6*, e2328136. https://doi.org/10.1001/jamanetworkopen.2023.28136. PMID: 37581887; PMCID: PMC10427943.
51. Najjari-Jamal, D.; Rovirosa, A.; Gimeno-Morales, M.; Majercakova, K.; Sánchez, M.; Garcia, S.; Guevara, D.; Muñoz, T.; De la Fuente, C.; Micó, S.; et al. Reirradiation Practice in Gynecological Cancer: Insights from a National Survey in Spain. *Clin. Transl. Oncol.* **2025**, *27*, 2494–2501. https://doi.org/10.1007/s12094-024-03804-x. PMID: 39636497.
52. Pollock, A.E.; Risher, H.; Berger, M.; Roque, D.M.; Rao, G.; Nichols, E.M.; Mohindra, P. Clinical Outcomes of Intensity Modulated Proton Therapy Reirradiation for Gynecologic Malignancies. *Adv. Radiat. Oncol.* **2023**, *8*, 101191. https://doi.org/10.1016/j.adro.2023.101191. PMID: 37213483; PMCID: PMC10196228.
53. Liu, H.; Chang, J.Y. Proton therapy in clinical practice. *Chin. J. Cancer* **2011**, *30*, 315–326. https://doi.org/10.5732/cjc.010.10529. PMID: 21527064; PMCID: PMC4013396.
54. Chakraborty, M.A.; Khan, A.J.; Cahlon, O.; Xu, A.J.; Braunstein, L.Z.; Powell, S.N.; Choi, J.I. Proton Reirradiation for High-Risk Recurrent or New Primary Breast Cancer. *Cancers* **2023**, *15*, 5722. https://doi.org/10.3390/cancers15245722. PMID: 38136268; PMCID: PMC10742022.
55. Beddok, A.; Willmann, J.; Embring, A.; Appelt, A.L.; Balermpas, P.; Chua, K.; Choi, J.I.; Elger, B.S.; Gabrys, D.; Hoskin, P.; et al. Reirradiation: Standards, challenges, and patient-focused strategies across tumor types. *CA Cancer J. Clin.* **2025**, *75*, 630–666. https://doi.org/10.3322/caac.70016. PMID: 40438993; PMCID: PMC12593330.
56. Mohamed, N.; Lee, A.; Lee, N.Y. Proton beam radiation therapy treatment for head and neck cancer. *Prec. Radiat. Oncol.* **2022**, *6*, 59–68. https://doi.org/10.1002/pro6.1135.
57. Yan, Y.; Alexander, D.A.; Bednarz, B.P.; Bronk, L.F.; Chen, H.; Gladstone, D.J.; Han, B.; Iannuzzi, C.M.; Li, Y.; Nguyen, N.; et al. Innovative approaches in precision radiation oncology: Advanced imaging technologies and challenges which shape the future of radiation therapy. *Front. Med.* **2025**, *12*, 1686593. https://doi.org/10.3389/fmed.2025.1686593. Erratum in *Front. Med.* **2025**, *12*, 1738811. https://doi.org/10.3389/fmed.2025.1738811. PMID: 41244760; PMCID: PMC12613237.
58. Verma, V.; Simone CB2nd Wahl, A.O.; Beriwal, S.; Mehta, M.P. Proton radiotherapy for gynecologic neoplasms. *Acta Oncol.* **2016**, *55*, 1257–1265. https://doi.org/10.1080/0284186X.2016.1205218. PMID: 27500710.

59. Candelaria, M.; Garcia-Arias, A.; Cetina, L.; Dueñas-Gonzalez, A. Radiosensitizers in cervical cancer. Cisplatin and beyond. *Radiat. Oncol.* **2006**, *1*, 15. https://doi.org/10.1186/1748-717X-1-15. PMID: 16722549; PMCID: PMC1479830.
60. Ladbury, C.; Germino, E.; Novak, J.; Liu, J.; Horne, Z.; Dyer, B.; Glaser, S. Combination radiation and immunotherapy in gynecologic malignancies-a comprehensive review. *Transl. Cancer Res.* **2021**, *10*, 2609–2619. https://doi.org/10.21037/tcr-20-3019. PMID: 35116574; PMCID: PMC8797685.
61. Zhou, L.; Liu, Q.; He, Y.; Tang, Y.; Liu, S.; Wang, X.; Shen, S.; Ji, J.; Liu, Z.; Zeng, X.; et al. Combining advanced radiotherapy techniques and immunotherapy: Immunomodulatory mechanisms and clinical prospects. *Front. Immunol.* **2026**, *17*, 1737661. https://doi.org/10.3389/fimmu.2026.1737661.
62. C. Kuipers, S.; Mvan Tuyll van Serooskerken, M.; Lathouwers, D.; Corbeau, A.; Mde Boer, S.; ANout, R.; SHoogeman, M.; Godart, J. Predicting lymphocyte dose and surviving fraction for VMAT and IMPT treatments with a dynamic lymphocyte flow model for locally advanced cervical cancer. *Phys. Med. Biol.* **2025**, *70*, 215005. https://doi.org/10.1088/1361-6560/ae0d29. PMID: 41022102.
63. Baumann, B.C.; Hallahan, D.E.; Michalski, J.M.; Perez, C.A.; Metz, J.M. Concurrent chemo-radiotherapy with proton therapy: Reduced toxicity with comparable oncological outcomes vs photon chemo-radiotherapy. *Br. J. Cancer* **2020**, *123*, 869–870. https://doi.org/10.1038/s41416-020-0919-2. PMID: 32555364; PMCID: PMC7493883.
64. Taş, E.E.; Ulgen, K.O. Predictive Modeling of Pharmacokinetic Drug-Drug and Herb-Drug Interactions in Oncology: Insights From PBPK Studies. *Int. J. Toxicol.* **2025**, *44*, 424–440. https://doi.org/10.1177/10915818251345116. PMID: 40499171; PMCID: PMC12397550.
65. Liu, H.; Zhang, Z.; Guo, X.; Wang, T.; Hu, J.; Shao, J.; Chi, F.; He, H. The Effect of Bladder and Rectum Volume Changes on Exposed Organ Volume During Intensity-Modulated Radiotherapy for Cervical Cancer. *Clin. Med. Insights Oncol.* **2025**, *19*, 11795549251377910. https://doi.org/10.1177/11795549251377910. PMID: 41000372; PMCID: PMC12457747.
66. Green, O.L.; Henke, L.E.; Hugo, G.D. Practical Clinical Workflows for Online and Offline Adaptive Radiation Therapy. *Semin. Radiat. Oncol.* **2019**, *29*, 219–227. https://doi.org/10.1016/j.semradonc.2019.02.004. PMID: 31027639; PMCID: PMC6487881.
67. Unkelbach, J.; Paganetti, H. Robust Proton Treatment Planning: Physical and Biological Optimization. *Semin. Radiat. Oncol.* **2018**, *28*, 88–96. https://doi.org/10.1016/j.semradonc.2017.11.005. PMID: 29735195; PMCID: PMC5942229.
68. Wang, D. A critical appraisal of the clinical utility of proton therapy in oncology. *Med. Devices* **2015**, *8*, 439–446. https://doi.org/10.2147/MDER.S65594. PMID: 26604838; PMCID: PMC4630192.
69. Global Proton Therapy Market Report. Available online: www.custommarketinsight.com (accessed on 10 February 2025).
70. Zhang, Q.; Yang, W.; Tan, L.; Guo, X.; Wang, T.; Zhu, P.; Jing, Z.; Ma, L.; Hou, J. Advances in proton therapy technology and global clinical applications. *Front. Oncol.* **2026**, *16*, 1718677. https://doi.org/10.3389/fonc.2026.1718677. PMID: 41756338; PMCID: PMC12932165.
71. The National Association of Proton Therapy. National Association for Proton Therapy (NAPT). Prior Authorization for Proton Therapy in 2025. Available online: https://proton-therapy.org/prior-authorization-for-proton-therapy-in-2025-what-providers-need-to-know/ (accessed on 1 January 2025).
72. Brown, M.H.; Pollock, A.E.; Sun, K.; Marter, K.; Alicia, D.; Li, E.; Risher, H.; Rao, G.G.; Roque, D.M.; Mohindra, P.; et al. Comparing Acute Toxicity of Proton and Photon Radiation Therapy in Newly Diagnosed Gynecologic Primaries. *Int. J. Radiat. Oncol. Biol. Phys.* **2026**, *124*, 1033–1041. https://doi.org/10.1016/j.ijrobp.2025.10.034. PMID: 41187862.
73. Chen, Z.; Dominello, M.M.; Joiner, M.C.; Burmeister, J.W. Proton versus photon radiation therapy: A clinical review. *Front. Oncol.* **2023**, *13*, 1133909. https://doi.org/10.3389/fonc.2023.1133909. PMID: 37064131; PMCID: PMC10091462.
74. Meixner, E.; Wark, A.; Forster, T.; Weykamp, F.; Lang, K.; König, L.; Lindel, K.; Oelmann-Avendano, J.T.; Krisam, J.; Schneeweiss, A.; et al. Health-related quality of life and patient-reported symptoms after postoperative proton beam radiotherapy of cervical and endometrial cancer: 2-year results of the prospective phase II APROVE-trial. *Radiat. Oncol.* **2023**, *18*, 5. https://doi.org/10.1186/s13014-023-02198-4. PMID: 36624483; PMCID: PMC9827629.
75. Paganetti, H. Range uncertainties in proton therapy and the role of Monte Carlo simulations. *Phys. Med. Biol.* **2012**, *57*, R99–R117. https://doi.org/10.1088/0031-9155/57/11/R99. PMID: 22571913; PMCID: PMC3374500.
76. Schuemann, J.; Dowdell, S.; Grassberger, C.; Min, C.H.; Paganetti, H. Site-specific range uncertainties caused by dose calculation algorithms for proton therapy. *Phys. Med. Biol.* **2014**, *59*, 4007–4031. https://doi.org/10.1088/0031-9155/59/15/4007. PMID: 24990623; PMCID: PMC4136435.
77. Albertini, F.; Matter, M.; Nenoff, L.; Zhang, Y.; Lomax, A. Online daily adaptive proton therapy. *Br. J. Radiol.* **2020**, *93*, 20190594. https://doi.org/10.1259/bjr.20190594. PMID: 31647313; PMCID: PMC7066958.

78. Lavrova, E.; Garrett, M.D.; Wang, Y.F.; Chin, C.; Elliston, C.; Savacool, M.; Price, M.; Kachnic, L.A.; Horowitz, D.P. Adaptive Radiation Therapy: A Review of CT-based Techniques. *Radiol. Imaging Cancer* **2023**, *5*, e230011. https://doi.org/10.1148/rycan.230011. PMID: 37449917; PMCID: PMC10413297.
79. Hörberger, F.; Andersson, K.M.; Enmark, M.; Kristensen, I.; Flejmer, A.; Edvardsson, A. Pencil beam scanning proton therapy for mediastinal lymphomas in deep inspiration breath-hold: A retrospective assessment of plan robustness. *Acta Oncol.* **2024**, *63*, 62–69. https://doi.org/10.2340/1651-226X.2024.23964. PMID: 38415848; PMCID: PMC11332452.
80. Kim, T.; Bizzocchi, N. Advancing proton therapy together: Insights on practice, technology, and implementation. *Tech. Innov. Patient Support Radiat. Oncol.* **2025**, *36*, 100350. https://doi.org/10.1016/j.tipsro.2025.100350. PMID: 41357997; PMCID: PMC12677061.
81. Duan, J.; Tao, C.; Wu, S.; Li, C.; Chen, J.; Dai, T.; Fan, Y.; Bai, T.; Meng, X.; Kong, T.; et al. Clinical advances and challenges in dose constraints for organs at risk in proton therapy: A systematic review of the last decade's literature. *Precis. Radiat. Oncol.* **2025**, *9*, 210–220. https://doi.org/10.1002/pro6.70020. PMID: 41164815; PMCID: PMC12559902.
82. Matuszak, N.; Suchorska, W.M.; Milecki, P.; Kruszyna-Mochalska, M.; Misiarz, A.; Pracz, J.; Malicki, J. FLASH radiotherapy: An emerging approach in radiation therapy. *Rep. Pract. Oncol. Radiother.* **2022**, *27*, 344–351. https://doi.org/10.5603/RPOR.a2022.0038. PMID: 36299375; PMCID: PMC9591027.
83. Teoh, M.; Clark, C.H.; Wood, K.; Whitaker, S.; Nisbet, A. Volumetric modulated arc therapy: A review of current literature and clinical use in practice. *Br. J. Radiol.* **2011**, *84*, 967–996. https://doi.org/10.1259/bjr/22373346. PMID: 22011829; PMCID: PMC3473700.
84. Wildman, V.L.; Wynne, J.F.; Momin, S.; Kesarwala, A.H.; Yang, X. Recent advances in applying machine learning to proton radiotherapy. *Biomed. Phys. Eng. Express* **2025**, *11*, 042005. https://doi.org/10.1088/2057-1976/adeb90. PMID: 40609552; PMCID: PMC12284894.
85. El Mjabber, R.; Alami, R.; Naim, A.; Kouhen, F.; Ismaili, N.; El Majjaoui, S.; Dahbi, Z. Bone Marrow-Sparing Pelvic Radiotherapy: Clinical Evidence, Dosimetric Constraints, and Clinical Outcomes. *Cureus* **2026**, *18*, e101210. https://doi.org/10.7759/cureus.101210. PMID: 41674757; PMCID: PMC12888062.
86. Distel, L.V.; Hildebrand, L.S.; Kuhlmann, L.C.F.; Vogel, R.K.G. Radiation sensitivity in genetic tumour syndromes and how to test for them. *Med. Genet.* **2025**, *37*, 313–320. https://doi.org/10.1515/medgen-2025-2041. PMID: 41210219; PMCID: PMC12594447.
87. Zhang, A.; Fan, L.; Liu, Q.; Zuo, X.; Zhu, J. Immunological Effects of Proton Radiotherapy: New Opportunities and Challenges in Cancer Therapy. *Cancer Innov.* **2025**, *4*, e70003. https://doi.org/10.1002/cai2.70003. PMID: 40061827; PMCID: PMC11885950.
88. Colaco, R.J.; Nichols, R.C.; Huh, S.; Getman, N.; Ho, M.W.; Li, Z.; Morris, C.G.; Mendenhall, W.M.; Mendenhall, N.P.; Hoppe, B.S. Protons offer reduced bone marrow, small bowel, and urinary bladder exposure for patients receiving neoadjuvant radiotherapy for resectable rectal cancer. *J. Gastrointest. Oncol.* **2014**, *5*, 3–8. https://doi.org/10.3978/j.issn.2078-6891.2013.041. PMID: 24490037; PMCID: PMC3904024.
89. New York Proton Center. New ASTRO Model Policy Expands Recommended Uses for Proton Therapy. Available online: https://www.nyproton.com/new-astro-model-policy-expands-recommended-uses-for-proton-therapy/ (accessed on 1 January 2025).
90. Particle Therapy Co-Operative Group North America (PTCOG-NA). Available online: https://www.ptcog-na.org/ (accessed on 11 February 2026).
91. Huang, D.; Frank, S.J.; Verma, V.; Thaker, N.G.; Brooks, E.D.; Palmer, M.B.; Harrison, R.F.; Deshmukh, A.A.; Ning, M.S. Cost-Effectiveness Models of Proton Therapy for Head and Neck: Evaluating Quality and Methods to Date. *Int. J. Part. Ther.* **2021**, *8*, 339–353. https://doi.org/10.14338/IJPT-20-00058.1. PMID: 34285960; PMCID: PMC8270103.
92. Miller, R.C.; Simone, B.A.; Lombardo, J.F.; Taylor, J.; Nowak-Choi, K.; Ko, K.; Ferguson, L.; Donnelly, A.; Ali, A.S.; Shi, W.; et al. A pilot trial using telemedicine in radiation oncology: The future of health care is virtual. *Telemed. Rep.* **2021**, *2*, 171–178.
93. Chetwood, J.D.; Ladep, N.G.; Taylor-Robinson, S.D. Research partnerships between high and low-income countries: Are international partnerships always a good thing? *BMC Med. Ethics* **2015**, *16*, 36. https://doi.org/10.1186/s12910-015-0030-z. PMID: 26017015; PMCID: PMC4447022.
94. Roy, E.; Chino, F.; King, B.; Madu, C.; Mattes, M.; Morrell, R.; Pollard-Larkin, J.; Siker, M.; Takita, C.; Ludwig, M. Increasing Diversity of Patients in Radiation Oncology Clinical Trials. *Int. J. Radiat. Oncol. Biol. Phys.* **2023**, *116*, 103–114. https://doi.org/10.1016/j.ijrobp.2022.11.044. PMID: 36526234; PMCID: PMC10414211.
95. Mohan, R.; Peeler, C.R.; Guan, F.; Bronk, L.; Cao, W.; Grosshans, D.R. Radiobiological issues in proton therapy. *Acta Oncol.* **2017**, *56*, 1367–1373. https://doi.org/10.1080/0284186X.2017.1348621. Erratum in *Acta Oncol.* **2019**, *58*, 132. https://doi.org/10.1080/0284186X.2018.1563380. PMID: 28826292; PMCID: PMC5842809.

96. Kuhn, T.M.; Dhanani, S.; Ahmad, S. An Overview of Endometrial Cancer with Novel Therapeutic Strategies. *Curr. Oncol.* **2023**, *30*, 7904–7919. https://doi.org/10.3390/curroncol30090574. PMID: 37754489; PMCID: PMC10528347.
97. Rabinovich, A.; Bernard, L.; Ramanakumar, A.V.; Stroian, G.; Gotlieb, W.H.; Lau, S.; Bahoric, B. Para-aortic and pelvic extended-field radiotherapy for advanced-stage uterine cancer: Dosimetric and toxicity comparison between the four-field box and intensity-modulated techniques. *Curr. Oncol.* **2015**, *22*, 405–411. https://doi.org/10.3747/co.22.2727. PMID: 26715873; PMCID: PMC4687661.
98. Lane, S.A.; Slater, J.M.; Yang, G.Y. Image-Guided Proton Therapy: A Comprehensive Review. *Cancers* **2023**, *15*, 2555. https://doi.org/10.3390/cancers15092555. PMID: 37174022; PMCID: PMC10177085.