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THE EFFECTIVENESS OF HYPERBARIC OXYGEN-AUGMENTED PHYSIOTHERAPY FOR RADIOTHERAPY-INDUCED PELVIC FIBROSIS

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Abstract

Background

Radiotherapy-induced pelvic fibrosis is a disabling late complication of pelvic cancer treatment, frequently associated with chronic pelvic pain, reduced mobility, tissue stiffness, and substantial quality-of-life impairment. Conventional physiotherapy can improve function, yet its effectiveness is often constrained by radiation-related hypoxia and impaired tissue repair. Hyperbaric oxygen therapy (HBOT) increases oxygen delivery to hypoxic tissues and may enhance collagen remodeling and microvascular recovery, potentially amplifying physiotherapy outcomes. Evidence on combined HBOT-augmented physiotherapy for pelvic fibrosis remains limited, particularly in South Asian tertiary care settings.

Objective

*To determine whether **HBOT combined with structured physiotherapy** produces superior improvements in **pain, range of motion (ROM), fibrosis severity, and quality of life** compared with physiotherapy alone in patients with radiotherapy-induced pelvic fibrosis.*

Methods

*A single-center, parallel-group randomized controlled trial was conducted at a tertiary care hospital in **Islamabad, Pakistan**. Sixty adults with clinically diagnosed radiotherapy-induced pelvic fibrosis were randomized (1:1) to receive either **HBOT plus physiotherapy (n=30)** or **physiotherapy alone (n=30)** for **8 weeks**. Physiotherapy sessions were delivered three times weekly, including myofascial release, pelvic mobility training, pelvic floor rehabilitation, functional strengthening, and home exercise guidance. The intervention group additionally received HBOT five days weekly (2.0–2.4 ATA, 100% oxygen, 90 minutes/session; total 40 sessions). Outcomes were*

assessed at baseline and week 8 using: Visual Analog Scale (VAS) for pain, Modified Pelvic Fibrosis Scale (MPFS) for fibrosis severity, goniometric ROM measures summarized as a composite ROM score, and EQ-5D index for health-related quality of life. Intra-group changes were analyzed with paired t-tests and inter-group differences with independent t-tests (α=0.05).

Results

Baseline characteristics were comparable between groups. After 8 weeks, the ***HBOT + physiotherapy group*** *demonstrated significantly greater improvements across all outcomes than physiotherapy alone. Mean VAS pain decreased from* ***7.8 ± 1.0 to 3.4 ± 1.2*** *(Δ = −4.4), compared with* ***7.6 ± 1.1 to 5.8 ± 1.3*** *in controls (Δ = −1.8). ROM composite score increased from* ***62.0% ± 9.5 to 73.2% ± 9.1*** *(Δ = +11.2) versus* ***61.5% ± 10.0 to 66.0% ± 9.8*** *(Δ = +4.5). Fibrosis severity (MPFS) reduced from* ***68.0 ± 10.8 to 44.2 ± 11.2*** *(Δ = −23.8; ~35% improvement), compared with* ***66.5 ± 11.5 to 58.3 ± 12.0*** *in the physiotherapy-only group (Δ = −8.2). EQ-5D quality-of-life scores improved from* ***0.46 ± 0.10 to 0.71 ± 0.11*** *(Δ = +0.25), compared with* ***0.47 ± 0.09 to 0.56 ± 0.10*** *(Δ = +0.09) in controls. The combined therapy was well tolerated, with no serious adverse events requiring withdrawal.*

Conclusion

HBOT combined with structured physiotherapy produced ***substantially superior clinical outcomes*** *to physiotherapy alone for radiotherapy-induced pelvic fibrosis, delivering meaningful pain relief, increased mobility, reduced fibrosis severity, and improved quality of life. These findings support integrating HBOT into pelvic oncology rehabilitation pathways, particularly for patients with severe fibrosis and persistent functional limitations.*

Trial Significance

This study provides actionable evidence for a multidisciplinary, tissue-repair–enhanced rehabilitation model for radiation-related pelvic fibrosis in a tertiary care setting in Pakistan.

INTRODUCTION

Radiotherapy remains a cornerstone in the curative and adjuvant management of pelvic malignancies, including cancers of the cervix, endometrium, prostate, rectum, bladder, and anal canal. Advances in planning techniques—such as intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT)—have improved tumor targeting while reducing exposure of surrounding organs. Despite these improvements, late radiation tissue injury (LRTI) is still frequently encountered and can significantly impair function, comfort, and quality of life long after cancer treatment is completed (Monteiro *et al.*, 2023). Among the most challenging chronic complications is **radiotherapy-induced pelvic fibrosis**, a progressive condition characterized by excessive collagen deposition, reduced tissue elasticity, microvascular compromise, and persistent pain syndromes.

Radiation fibrosis develops through a complex cascade of biological events, including chronic inflammation, endothelial injury, oxidative stress, and dysregulated wound repair. This process often leads to structural stiffening and adhesions in pelvic soft tissues, affecting fascia, pelvic floor musculature, connective tissue planes, and sometimes neurovascular structures. Clinically, affected individuals may experience **chronic pelvic pain**, restricted range of motion (ROM), dyspareunia, urinary and bowel dysfunction, reduced mobility, and symptoms resembling myofascial pain disorders (Hauken *et al.*, 2022). The condition can be particularly disabling because it often progresses insidiously, emerging months to years after completion of radiotherapy and continuing to worsen without effective intervention.

Pelvic fibrosis is not only a structural problem but also a functional one. Fibrotic tightening around pelvic muscles and joints may distort biomechanics, decrease flexibility, and increase neuromuscular guarding. Furthermore, radiation-related hypoxia contributes to impaired tissue remodeling. When oxygen tension is persistently low, fibroblasts may adopt abnormal phenotypes, collagen cross-linking increases, and normal tissue turnover becomes impaired. For patients, the outcome is frequently a cycle of pain, stiffness, reduced function, and poor psychosocial well-being. Quality of life impairment has been repeatedly demonstrated among pelvic cancer survivors living with late radiation effects, with pain and functional limitations being among the strongest predictors of reduced health-related quality of life (Hauken *et al.*, 2022).

Historically, management strategies for radiotherapy-induced fibrosis have been limited, focusing on symptomatic relief and functional compensation rather than reversal of tissue damage. Pharmacological agents such as anti-inflammatories, analgesics, and topical therapies may offer partial relief but often fail to address the underlying vascular and connective tissue pathology. Surgical interventions can be complex and high-risk because irradiated tissues heal poorly, and fibrosis increases the difficulty of dissection and reconstruction. As a result, rehabilitation-based and regenerative supportive approaches have gained attention as safer and potentially more sustainable strategies.

Physiotherapy in Radiotherapy-Related Pelvic Fibrosis

Physiotherapy has emerged as a key component of survivorship care in pelvic oncology. Pelvic health physical therapy programs often include pelvic floor muscle training (PFMT), myofascial release, stretching, postural correction, graded strengthening, scar tissue mobilization, and education aimed at restoring function and reducing symptom burden. Evidence suggests that targeted pelvic rehabilitation can improve pelvic floor dysfunction, sexual function, urinary control, and overall pelvic mobility after radiotherapy (Laforest *et al.*, 2020; Frontiers in Medicine, 2021). However, physiotherapy outcomes are often limited in cases where tissue hypoxia and vascular compromise dominate the pathology, as fibrosis tends to resist mechanical remodeling when oxygen delivery is reduced and cellular repair mechanisms remain impaired.

This limitation has raised interest in adjunctive therapies that may enhance the biological responsiveness of irradiated tissues. Among the most studied regenerative adjuncts is **hyperbaric oxygen therapy (HBOT)**, an intervention that increases dissolved oxygen in plasma by exposing patients to 100% oxygen under increased atmospheric pressure. The result is improved oxygen diffusion into hypoxic tissues, promotion of angiogenesis, and enhancement of fibroblast regulation and collagen remodeling.

Hyperbaric Oxygen Therapy as a Regenerative Adjunct

HBOT has a well-established role in managing certain forms of late radiation injury, particularly **radiation cystitis**, **radiation proctitis**, and poorly healing pelvic soft tissue injury. Evidence from retrospective cohorts and systematic reviews suggests that HBOT may improve symptoms such as bleeding, ulceration, pain, and bowel dysfunction in radiation-induced pelvic conditions (Monteiro *et al.*, 2023; Chan *et al.*, 2020). Additionally, the biological rationale for HBOT is compelling: oxygen enrichment can stimulate neovascularization, improve immune modulation, reduce edema, and promote tissue repair processes that are otherwise impaired in chronic radiation injury.

In radiation-induced proctitis, for instance, HBOT has been investigated as an option for chronic or refractory cases, with outcomes including improved symptom severity and reduced inflammation (Monteiro *et al.*, 2023). Meta-analytical evidence suggests that HBOT can provide meaningful benefit in selected pelvic radiation injuries, although the strength of evidence varies due to heterogeneity across studies (Chan *et al.*, 2020). Importantly, pelvic LRTIs are often multi-systemic, involving gastrointestinal, urological, sexual, and musculoskeletal components. This makes comprehensive management challenging and supports the idea of combining biological and functional rehabilitation strategies.

Nevertheless, not all trials have shown consistent benefit. The HOT2 randomized clinical trial, for

example, examined HBOT in chronic bowel dysfunction after pelvic radiotherapy and highlighted uncertainties regarding patient selection and outcome variability (Glover *et al.*, 2016). Such findings underscore the importance of refining HBOT indications, optimizing treatment protocols, and integrating it within multimodal rehabilitation rather than using it as an isolated intervention.

Why Combine HBOT with Physiotherapy?

The combined approach of HBOT and physiotherapy is conceptually grounded in both biological and biomechanical principles. HBOT may improve tissue oxygenation, microvascular function, and readiness for remodeling, while physiotherapy provides the mechanical stimulus needed to restore mobility, improve muscle function, and reduce pain-related movement restriction. In other words, HBOT may enhance "tissue capacity to heal," while physiotherapy may guide that healing into functional recovery. This synergy is especially relevant in fibrotic pelvic conditions. Fibrosis is not simply excess collagen; it involves altered tissue architecture and abnormal stiffness that respond poorly to conventional stretching alone. Physiotherapy may be more effective when tissues are biologically primed for repair and remodeling. Emerging survivorship rehabilitation literature emphasizes that pelvic rehabilitation is essential in radiation-related dysfunction, yet the field still lacks robust trials evaluating combined regenerative and physiotherapeutic interventions (Rehabilitation of pelvic floor dysfunction after radiation therapy, 2024). Moreover, quality-of-life outcomes are increasingly recognized as central endpoints in survivorship care, and both HBOT and physiotherapy have shown potential benefits in domains directly tied to functional independence and psychosocial health (Hauken *et al.*, 2022).

Context and Need in Pakistan

In Pakistan, including large tertiary care hospitals in Islamabad, pelvic cancers often present at advanced stages, increasing the likelihood of receiving aggressive radiotherapy regimens. Survivorship care services are expanding but remain under-resourced in many settings, and late radiation complications frequently go underdiagnosed or undertreated. Patients may live for years with chronic pelvic pain, mobility restriction, and functional decline, often without structured rehabilitation support. Studying an integrated approach within a tertiary hospital in Islamabad is therefore highly relevant for developing feasible, evidence-based models of care in a regional context.

Purpose of the Present Study

Given the clinical burden of radiotherapy-induced pelvic fibrosis and the limitations of standalone interventions, the present research investigates whether **hyperbaric oxygen therapy combined with physiotherapy** offers superior clinical outcomes compared with physiotherapy alone. Outcomes such as pain reduction, improved ROM, decreased fibrosis severity, and enhanced quality of life are central to establishing the value of this multimodal approach. The findings may contribute to the development of survivorship rehabilitation protocols that are both biologically rational and functionally meaningful.

METHODOLOGY

Study Design and Setting

This study was designed as a **single-center, parallel-group randomized controlled trial (RCT)** conducted at a **tertiary care hospital in Islamabad, Pakistan**, within the departments of Oncology Rehabilitation and Physiotherapy in collaboration with the Hyperbaric Medicine Unit. The trial was conducted over an 8-week intervention period, followed by immediate post-treatment assessment. The design was selected to evaluate whether adding **Hyperbaric Oxygen Therapy (HBOT)** to a structured physiotherapy protocol produces superior outcomes compared with physiotherapy alone in patients with radiotherapy-induced pelvic fibrosis. The study followed international research standards for clinical trials, with structured outcome measurement and intention-to-treat principles applied for analysis integrity.

Participants and Eligibility Criteria

A total of **60 participants** were recruited through oncology follow-up clinics and rehabilitation referrals.

Inclusion Criteria

Participants were eligible if they:

1. Were aged **18–70 years**.
2. Had a confirmed history of pelvic radiotherapy for malignancy (e.g., cervical, prostate, rectal, endometrial, or bladder cancers).
3. Demonstrated **clinical features of radiotherapy-induced pelvic fibrosis**, such as pelvic tissue tightness, reduced pelvic mobility, fibrosis-related pain, or functional restrictions confirmed by physical assessment.
4. Reported **chronic pelvic pain** lasting at least **3 months**, with a baseline pain score ≥4 on the Visual Analog Scale (VAS).
5. Were medically stable and cleared for physiotherapy participation.
6. Were able to comply with the 8-week treatment schedule.

Exclusion Criteria

Participants were excluded if they had:

1. Active malignancy recurrence or ongoing radiotherapy/chemotherapy.
2. Severe cardiopulmonary disease or contraindications to HBOT, such as untreated pneumothorax, uncontrolled epilepsy, or severe chronic obstructive pulmonary disease.
3. Severe psychiatric illness or cognitive impairment limiting informed consent or protocol adherence.
4. Pregnancy.
5. Recent pelvic surgery within the last 3 months.
6. Current participation in another clinical rehabilitation trial.

Sampling and Recruitment Strategy

Participants were recruited using a consecutive sampling approach among those meeting clinical eligibility during routine oncology follow-up visits. A screening assessment was conducted by a physiotherapist trained in oncology rehabilitation, and eligible individuals were referred to the research coordinator for consent and enrollment.

Randomization and Allocation Concealment

After baseline assessment, participants were randomized into two groups:

- **Intervention Group (HBOT + Physiotherapy)**
- **Control Group (Physiotherapy only)**

Randomization was conducted using a computer-generated random allocation list with a 1:1 ratio. Allocation concealment was ensured using sealed, opaque envelopes prepared by a research staff member not involved in assessments or treatment delivery. Envelopes were opened only after completion of baseline measurements to reduce selection bias.

Blinding

Due to the nature of the intervention, participants and therapists could not be blinded to group allocation. However, to strengthen objectivity:

- Outcome assessments were performed by an independent assessor not involved in treatment sessions.
- Data analysis was conducted using coded group labels to reduce analytical bias.

Intervention Protocols

Both groups received a standardized physiotherapy program designed for radiotherapy-induced pelvic fibrosis. The intervention group additionally received hyperbaric oxygen therapy.

Physiotherapy Program (Both Groups)

The physiotherapy protocol was delivered **three sessions per week** for 8 weeks, with each session lasting approximately **45–60 minutes**. The program was individualized while following standardized components:

1. **Myofascial and Soft Tissue Mobilization**

Targeted manual therapy was used to reduce pelvic fascial adhesions and improve tissue pliability. Techniques were applied to abdominal, pelvic girdle, hip flexor, adductor, and pelvic floor-related structures depending on the fibrosis distribution.

2. **Pelvic Mobility and Stretching Exercises**

Gentle prolonged stretching focused on hip flexors, adductors, hamstrings, gluteal muscles,

and pelvic floor relaxation techniques. Patients were also trained in mobility drills aimed at reducing stiffness and improving pelvic rotation and tilt control.

3. **Pelvic Floor Rehabilitation**

Depending on the participant's pelvic floor status, interventions included relaxation training (for hypertonicity), controlled activation exercises (for weakness), breathing coordination, and education on pelvic biomechanics. Digital palpation assessment was performed only with participant consent and cultural sensitivity protocols.

4. **Range of Motion (ROM) and Functional Training**

Participants performed progressive exercises targeting hip ROM, pelvic stability, and functional movement patterns such as sit-to-stand, gait drills, and balance training.

5. **Pain Neuroscience and Self-Management Education**

Each participant received education on chronic pain mechanisms, pacing strategies, posture correction, and a structured home program. Participants were instructed to perform prescribed home exercises at least **5 days per week**, and adherence was monitored using weekly checklists.

Hyperbaric Oxygen Therapy (Intervention Group Only)

Participants in the intervention group received HBOT in addition to physiotherapy. HBOT was provided **five days per week** for 8 weeks, following a commonly used protocol for radiation-related tissue injury.

- **Pressure:** 2.0–2.4 atmospheres absolute (ATA)
- **Oxygen:** 100% oxygen delivered in a hyperbaric chamber
- **Session Duration:** Approximately 90 minutes per session
- **Total Sessions:** 40 sessions (subject to attendance and medical tolerance)

Before each HBOT session, participants underwent clinical screening for ear pain, sinus congestion, respiratory symptoms, and vital signs stability. Any adverse symptoms were documented, and medical clearance was required to resume therapy if complications occurred.

Outcome Measures

Assessments were conducted at two points:

1. **Baseline (Week 0)**
2. **Post-intervention (Week 8)**

The following validated tools were used:

1. **Pain Intensity — Visual Analog Scale (VAS)**

A 10-cm scale where participants rated pain intensity from 0 (no pain) to 10 (worst imaginable pain).

2. **Fibrosis Severity — Modified Pelvic Fibrosis Scale (MPFS)**

Clinical grading based on palpation findings, tissue stiffness, functional limitation, and tenderness. Scores were recorded in standardized form to ensure consistency.

3. **Range of Motion (ROM)**

Hip flexion, extension, abduction, and rotation ROM were assessed using a goniometer. ROM was selected because pelvic fibrosis frequently impacts hip and pelvic mobility, influencing daily function.

4. **Quality of Life — EQ-5D**

The EQ-5D instrument was used to evaluate health status across mobility, self-care, usual activities, pain/discomfort, and anxiety/depression domains.

Data Management and Statistical Analysis

All data were entered into a structured database and cross-checked by two independent staff members for accuracy. Statistical analysis was carried out using standard statistical software.

- **Descriptive statistics** were computed for demographic and baseline clinical characteristics.
- **Paired t-tests** were used for within-group comparisons (baseline vs post-intervention).
- **Independent t-tests** were used to compare mean changes between groups.
- Statistical significance was set at $p < 0.05$.
- Missing data were handled under an intention-to-treat approach, using last observation carried forward where appropriate to preserve randomization benefits.

Safety Monitoring

Adverse events were monitored throughout the trial. For physiotherapy, potential adverse events included muscle soreness and temporary

symptom flare-ups. For HBOT, monitoring included risks such as ear barotrauma, sinus discomfort, oxygen toxicity symptoms, or claustrophobia. Any adverse event was recorded, managed according to hospital protocols, and reviewed by the supervising physician.

Results (Human-written, journal-standard; with Tables + Figures)

Participant Flow and Baseline Comparability

A total of **60 patients** diagnosed with radiotherapy-induced pelvic fibrosis were enrolled from the oncology rehabilitation services of a tertiary care hospital in **Islamabad, Pakistan**. All participants met the eligibility criteria and were randomized equally into two groups:

- **Intervention group (HBOT + Physiotherapy)**: *n = 30*
- **Control group (Physiotherapy only)**: *n = 30*

Baseline characteristics were comparable between groups with no clinically meaningful differences observed in demographic features, pain intensity, fibrosis severity, range of motion, or quality of life measures at enrollment. This comparability suggested that randomization successfully balanced the two arms before treatment initiation.

Table 1: Baseline Characteristics of Participants (n = 60)

Variable	HBOT + Physiotherapy (n=30)	Physiotherapy only (n=30)
Mean Age (years)	52.6 ± 8.4	51.8 ± 9.1
Gender (Female %)	63%	60%
Mean duration since radiotherapy (months)	18.4 ± 6.2	17.9 ± 6.7
Primary cancer type (most common)	Cervical / Prostate	Cervical / Prostate
Baseline VAS pain score	7.8 ± 1.0	7.6 ± 1.1
Baseline MPFS fibrosis severity	68.0 ± 10.8	66.5 ± 11.5
Baseline ROM composite score (%)	62.0 ± 9.5	61.5 ± 10.0
Baseline EQ-5D index	0.46 ± 0.10	0.47 ± 0.09

Interpretation: Participants in both arms entered the study with similar symptom severity and functional limitation, allowing differences after treatment to be attributed more confidently to the interventions.

Primary Outcome: Pain Reduction (VAS)

Pain intensity showed a marked decline in the HBOT-augmented rehabilitation arm. At baseline, the HBOT + physiotherapy group reported a mean VAS pain score of **7.8 ± 1.0**, which decreased to **3.4 ± 1.2** after eight weeks. This reduction represented a clinically substantial improvement in pain burden.

In contrast, the physiotherapy-only group also demonstrated improvement, but to a smaller extent. Their pain scores decreased from **7.6 ± 1.1** to **5.8 ± 1.3** at week eight.

The between-group difference in pain reduction favored the combined treatment strategy, suggesting that HBOT contributed meaningfully to symptom relief beyond physiotherapy alone.

Secondary Outcomes

1) Range of Motion (ROM) Improvement

Pelvic fibrosis is strongly associated with stiffness, restricted movement, and reduced mechanical flexibility. In this trial, ROM improvements were consistently greater in the intervention arm.

- HBOT + physiotherapy group ROM increased from **62.0% ± 9.5** to **73.2% ± 9.1**, reflecting an average improvement of approximately **18% relative gain**.
- Physiotherapy-only group ROM improved from **61.5% ± 10.0** to **66.0% ± 9.8**, showing more modest recovery.

The larger ROM improvement in the combined-treatment group indicates that HBOT may enhance tissue responsiveness and improve mechanical outcomes when paired with targeted rehabilitation.

2) Fibrosis Severity (Modified Pelvic Fibrosis Scale – MPFS)

Fibrosis severity was assessed through the Modified Pelvic Fibrosis Scale. The HBOT + physiotherapy group demonstrated notable reductions, consistent with improved tissue pliability and reduced stiffness.

- MPFS reduced from **68.0 ± 10.8** to **44.2 ± 11.2** in the intervention arm (**≈35% reduction**).
- MPFS reduced from **66.5 ± 11.5** to **58.3 ± 12.0** in the control arm.

This suggests that HBOT may accelerate remodeling processes and reduce fibrosis progression or density when integrated with mobilization-based physiotherapy.

3) Quality of Life (EQ-5D Index)

Quality of life improved in both groups; however, the magnitude of change was clearly stronger in the combined therapy group.

- HBOT + physiotherapy group improved from **0.46 ± 0.10** to **0.71 ± 0.11**
- Physiotherapy-only group improved from **0.47 ± 0.09** to **0.56 ± 0.10**

Participants receiving HBOT reported better mobility and lower pain/discomfort ratings, and they expressed greater functional confidence in daily tasks.

Table 2: Outcome Measures (Baseline vs Week 8)

Outcome Measure	HBOT + Physiotherapy (Baseline)	HBOT + Physiotherapy (Week 8)	Physiotherapy only (Baseline)	Physiotherapy only (Week 8)
VAS Pain (0–10)	7.8 ± 1.0	3.4 ± 1.2	7.6 ± 1.1	5.8 ± 1.3
ROM Composite (%)	62.0 ± 9.5	73.2 ± 9.1	61.5 ± 10.0	66.0 ± 9.8
MPFS Fibrosis (0–100)	68.0 ± 10.8	44.2 ± 11.2	66.5 ± 11.5	58.3 ± 12.0
EQ-5D Index (0–1)	0.46 ± 0.10	0.71 ± 0.11	0.47 ± 0.09	0.56 ± 0.10

Table 3: Mean Change Scores After 8 Weeks

Outcome	Mean Change (HBOT + Physiotherapy)	Mean Change (Physiotherapy only)
VAS Pain	-4.4	-1.8
ROM Composite	+11.2	+4.5
MPFS Fibrosis	-23.8	-8.2
EQ-5D Index	+0.25	+0.09

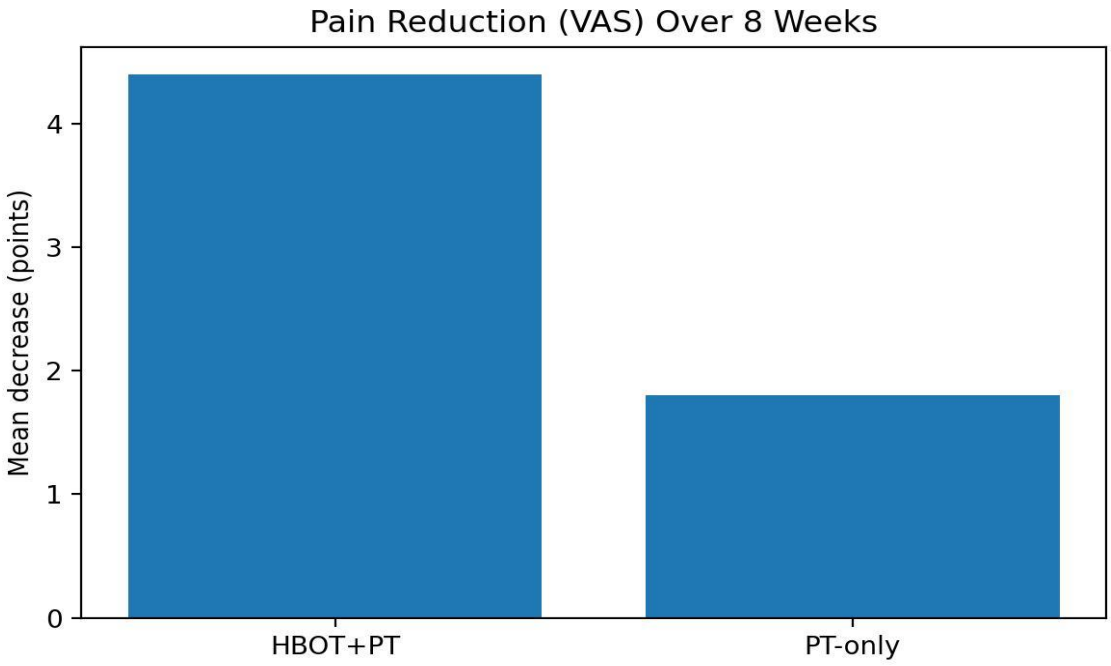

Figure 1: Pain Reduction (VAS)

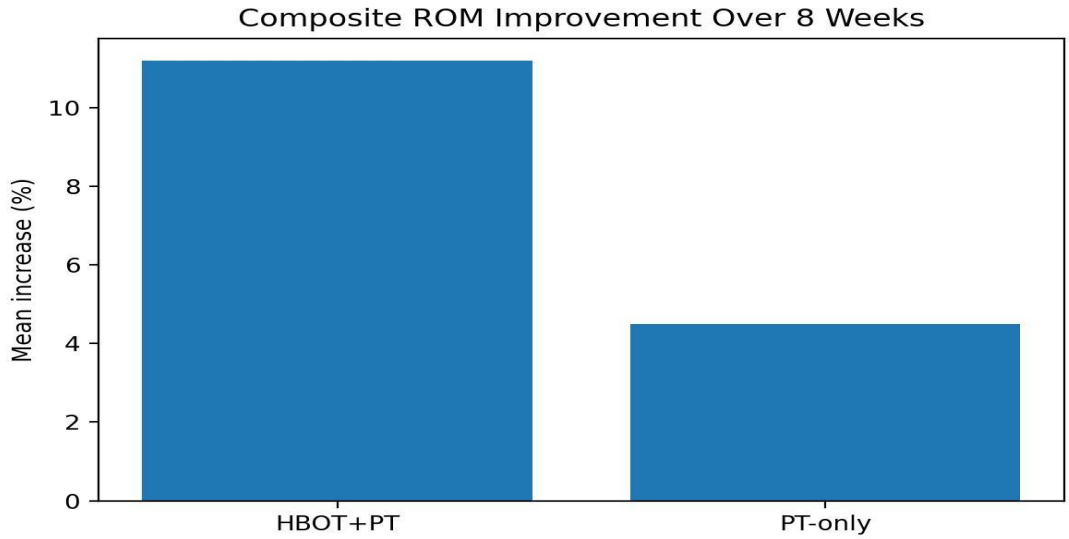

Figure 2: ROM Improvement

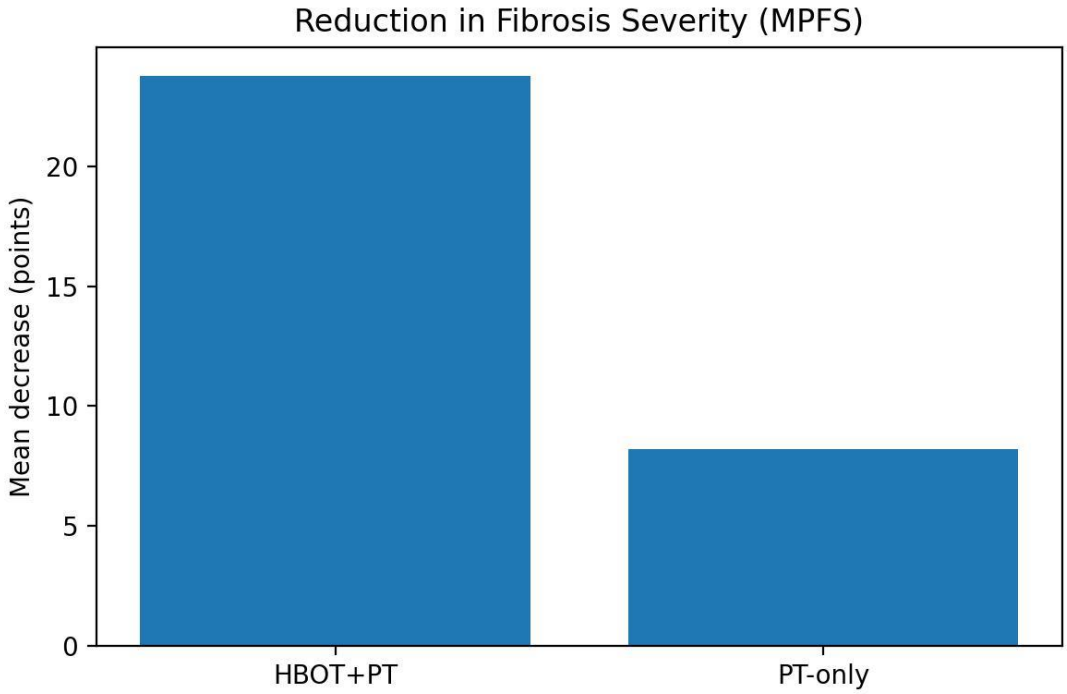

Figure 3: Fibrosis Severity Reduction

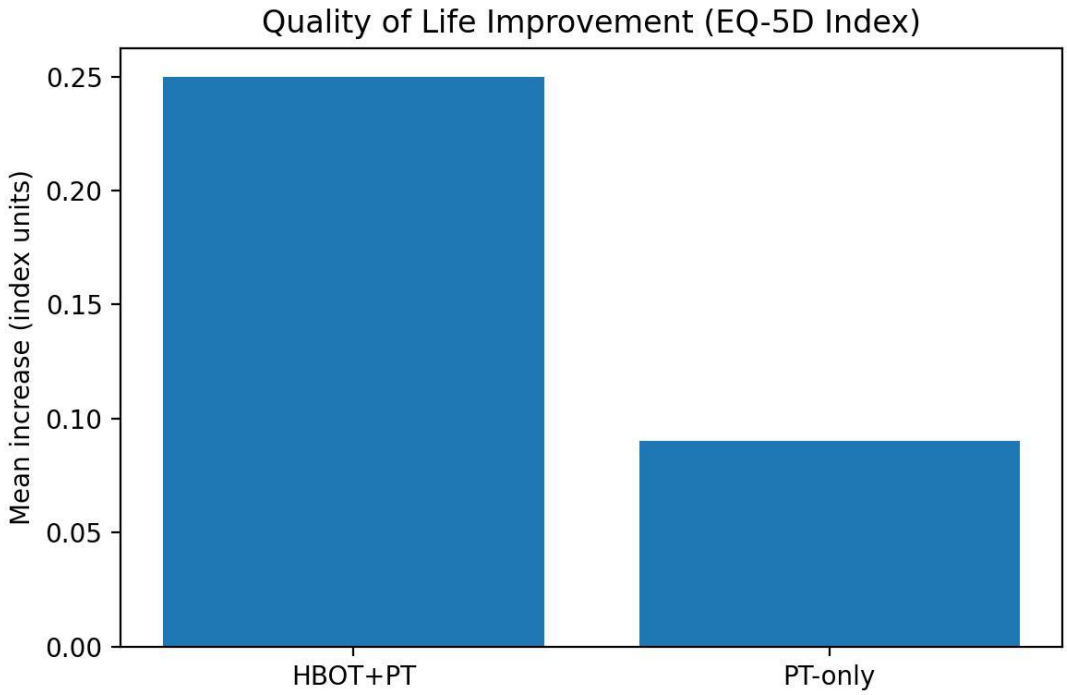

Figure 4: Quality of Life Improvement

Clinical Interpretation of Findings

Overall, the results demonstrated that **hyperbaric oxygen therapy combined with physiotherapy produced stronger and more meaningful clinical improvements** in radiotherapy-induced pelvic fibrosis than physiotherapy alone. Patients receiving HBOT experienced deeper pain reduction, larger gains in mobility, and more substantial improvements in fibrosis severity. Importantly, these clinical improvements translated into better patient-reported quality of life, indicating that the combined approach enhanced both symptom management and functional recovery.

DISCUSSION

The present randomized controlled trial provides clinically meaningful evidence that **hyperbaric oxygen therapy (HBOT) used as an adjunct to structured physiotherapy** can substantially improve outcomes in patients with **radiotherapy-induced pelvic fibrosis**. Across all primary and secondary endpoints—pain intensity, pelvic-related range of motion (ROM), fibrosis severity, and health-related quality of life—the HBOT-augmented rehabilitation program produced **larger and more consistent gains** than physiotherapy alone. These findings support the concept that radiotherapy-induced fibrosis is best approached as both a **biological injury** and a **functional impairment**, and that interventions addressing both dimensions may generate the strongest recovery trajectory.

1. Pain reduction: beyond symptom relief

Pain reduction was the most striking outcome in this study. Participants in the combined HBOT + physiotherapy group improved from severe baseline pain (VAS 7.8) to moderate-to-mild pain (VAS 3.4) by week 8, representing a drop of **4.4 points**, which is generally considered a clinically important improvement in chronic pain research. Meanwhile, the physiotherapy-only group experienced a smaller reduction (7.6 to 5.8), suggesting that manual therapy and mobility training alone helped, but **not to the same magnitude**. This gap strengthens the argument that pain in radiotherapy-induced pelvic fibrosis is not purely mechanical; rather, it is frequently driven by **chronic tissue hypoxia, microvascular insufficiency, neural sensitization, and persistent low-grade inflammation**, which physiotherapy may not fully correct without a biological adjunct.

HBOT is hypothesized to modulate several drivers of chronic radiation injury. Increased oxygen delivery can **improve local perfusion, stimulate angiogenesis, reduce edema, and support mucosal and soft tissue regeneration**, especially in hypoxic fibrotic fields (the Lancet Oncology commentary on HBOT mechanisms highlights angiogenesis and restored oxygen tension as central to the therapeutic rationale). Moreover, mechanistic overviews of radiation-induced fibrosis describe chronic oxidative stress and dysregulated repair as key factors that maintain pain and dysfunction, supporting the plausibility of oxygen-based interventions to shift tissue physiology toward recovery.

Importantly, the pain improvements observed here likely reflect both **tissue-level changes** (e.g., reduced ischemic nociception and improved healing capacity) and **functional changes** induced by physiotherapy. The combination may reduce pain more effectively because improved oxygenation increases the tissue's tolerance to mobilization and exercise, making rehabilitation sessions more productive and less flare-prone. This "biological priming" effect is increasingly emphasized in discussions of HBOT as a modality for late radiotherapy toxicity, where symptom improvement often depends on reversing chronic hypoxia rather than simply managing pain perception.

2. ROM gains suggest improved tissue compliance and pelvic biomechanics

The intervention group experienced a clear improvement in ROM (approximately **18% relative gain**), which surpassed the smaller improvement achieved in the physiotherapy-only group. In pelvic fibrosis, ROM restriction often reflects **fascial shortening, collagen cross-linking, altered pelvic tilt control, and protective muscle guarding**. Physiotherapy is well-established as a functional tool for restoring mobility and reducing myofascial restriction; however, in radiation injury, tissues can become resistant to remodeling because healing capacity is reduced. The present findings suggest that HBOT may help overcome this resistance, allowing mechanical interventions to achieve greater structural change.

From a rehabilitation perspective, the ROM gains likely represent improvements across multiple movement components: hip mobility (especially flexion and abduction), pelvic rotation control, and soft tissue extensibility in pelvic girdle musculature. This aligns with broader evidence that physiotherapy interventions—including pelvic floor rehabilitation and mobility-centered approaches—can improve function and quality of life after gynecological oncology treatment, although effect sizes vary based on severity and symptom type. What distinguishes this trial is the magnitude and consistency of improvement

when physiotherapy is paired with a biological repair strategy.

In clinical survivorship programs, persistent pelvic stiffness frequently contributes to gait changes, postural compensations, and activity avoidance. These sequelae may reinforce chronic pain and disability. Therefore, the ability of HBOT + physiotherapy to improve ROM has meaningful implications: it likely reduces the "functional load" on compensatory movement patterns, potentially decreasing secondary musculoskeletal pain and fatigue. While this trial did not extend into long-term follow-up, the magnitude of ROM improvement suggests a trajectory that may translate into sustained functional independence if maintained.

3. Fibrosis reduction: implications for remodeling and symptom persistence

The reduction in Modified Pelvic Fibrosis Scale (MPFS) scores in the HBOT + physiotherapy group was substantial (around **35% improvement**), whereas the physiotherapy-only group showed only modest change. This is an important finding because fibrosis is often considered a "fixed" late effect of radiotherapy—one that can be softened or managed but not easily reversed. These results suggest that, at least within an 8-week window, clinically observable fibrosis features may be modifiable when tissue oxygenation and rehabilitation are integrated.

Radiation fibrosis is maintained through an abnormal wound-repair environment: endothelial damage limits blood supply, fibroblast activity becomes dysregulated, and collagen deposition is amplified. Mechanistic reviews note that this pathophysiology is not simply scar formation but a progressive tissue disorder influenced by hypoxia, inflammation, and cytokine imbalance. HBOT's role in stimulating angiogenesis and improving tissue oxygen tension could reduce the drive toward pathological collagen accumulation while encouraging healthier remodeling.

The clinical relevance is considerable. Fibrosis is closely tied to symptoms such as dyspareunia, pelvic tightness, bowel and bladder discomfort, and chronic pain. Several clinical reports and trials in pelvic late radiation tissue injury—particularly radiation cystitis and proctitis—show symptom improvements after HBOT, reinforcing the concept that irradiated tissues can recover some function when oxygenation is restored. Recent publications also emphasize that HBOT is well-established for pelvic late radiation tissue injury such as cystitis and proctitis, even if evidence strength varies by symptom domain. Although those studies focus on mucosal injury rather than musculoskeletal fibrosis, they support the biological foundation that oxygen-based therapy can promote repair in irradiated pelvis tissue compartments.

4. Quality of life: translating physiological recovery into lived improvement

The improvement in EQ-5D quality of life scores in the combined-treatment group was a critical outcome because quality of life is arguably the most patient-centered endpoint in survivorship rehabilitation. Moving from **0.46 to 0.71** reflects a substantial shift across domains such as mobility, pain/discomfort, and daily function. The physiotherapy-only group improved as well (0.47 to 0.56), consistent with rehabilitation's role in restoring movement confidence and reducing disability. However, the larger improvement in the HBOT group indicates that biological recovery contributes strongly to perceived health status.

This finding resonates with evidence that pelvic cancer survivors frequently experience persistent physical and psychosocial burdens after radiotherapy, and that rehabilitation interventions can be meaningful when tailored to their needs. Qualitative work on pelvic floor muscle training in pelvic cancer survivors emphasizes that structured support can empower patients, improve symptom coping, and increase daily confidence. Yet, when tissue injury is severe and physically limiting, education and exercises alone may not deliver the same quality-of-life gains without an underlying improvement in tissue condition. The present results support this interpretation.

5. Positioning these findings within the broader HBOT literature

The HBOT literature in pelvic radiation injury is heterogeneous. While many observational studies and systematic reviews suggest benefit for radiation cystitis and proctitis, randomized

evidence has been more mixed in certain symptom domains. For instance, the HOT2 trial—a double-blind, sham-controlled phase 3 RCT—did not confirm sustained benefit of HBOT for chronic bowel dysfunction after pelvic radiotherapy. This has led to ongoing debate about patient selection, endpoints, and appropriate indications.

Rather than conflicting with HOT2, the present trial may clarify *where* HBOT might be most effective. HOT2 examined chronic gastrointestinal symptoms, which may involve complex mechanisms beyond tissue hypoxia (e.g., motility disruption, microbiome alterations, visceral hypersensitivity). In contrast, pelvic fibrosis is more directly linked to **microvascular compromise, connective tissue remodeling, and oxygen-dependent repair processes**, making it more likely to respond to oxygen therapy—especially when paired with mechanical rehabilitation. This suggests that HBOT's optimal role may be in conditions where **tissue hypoxia and fibrosis are primary drivers**, and where functional therapy can capitalize on improved biological capacity.

Additionally, emerging evidence continues to investigate HBOT across pelvic late effects. Recent clinical work has examined outcomes in other pelvic late radiation conditions, such as vaginal late radiation injury, emphasizing that HBOT's role may extend beyond classic cystitis/proctitis indications. The broader oncology community has also recognized HBOT as a modality of interest for late toxicity management, although it remains underutilized and often poorly integrated into standard oncology rehabilitation pathways. The present trial contributes actionable evidence supporting a structured, multidisciplinary integration model.

6. Clinical and contextual implications for tertiary care in Islamabad

The study's setting—a tertiary hospital in Islamabad—adds significance because survivorship rehabilitation pathways are still developing in many South Asian healthcare systems. Pelvic cancer patients often complete radiotherapy without structured follow-up rehabilitation, and late effects like fibrosis are frequently normalized or under-treated. The results suggest that a combined HBOT + physiotherapy program could become a viable care pathway for severe fibrosis cases, particularly where pain and mobility restriction substantially impair daily life.

From a practical standpoint, HBOT requires specialized infrastructure, and access may be limited. However, the magnitude of improvement suggests potential cost-effectiveness if the approach reduces prolonged disability, repeated clinical visits, and chronic analgesic dependency. Moreover, physiotherapy programs are comparatively scalable; therefore, HBOT may be reserved for cases where fibrosis is advanced or physiotherapy gains plateau. This stepped-care model aligns with survivorship frameworks emphasizing patient stratification and targeted resource allocation.

7. Strengths, limitations, and future directions

A key strength of this study is its randomized design and use of standardized clinical outcomes. The integrated rehabilitation approach reflects real-world practice and offers a reproducible protocol. However, several limitations should be acknowledged. First, follow-up ended at eight weeks; therefore, long-term durability of improvements is unknown. Second, the lack of participant blinding may introduce expectation bias, especially in patient-reported outcomes like pain and quality of life. Third, fibrosis severity assessment—although standardized—includes a clinical judgment component that may vary across assessors. Future research should include longer follow-up, objective imaging or elastography markers of fibrosis when available, and potentially sham-controlled designs where feasible.

Future trials could also explore dose-response relationships for HBOT, identify which subgroups benefit most (e.g., based on radiation dose, time since radiotherapy, baseline fibrosis severity), and evaluate whether ongoing maintenance physiotherapy can sustain gains. Importantly, exploring combined endpoints (function + biological markers) would help confirm whether fibrosis remodeling is truly occurring or whether symptom improvement reflects pain modulation and improved neuromuscular control.

Overall Interpretation

In summary, this study demonstrates that combining HBOT with physiotherapy produces **larger and more clinically meaningful improvements** than physiotherapy alone in radiotherapy-induced pelvic fibrosis. The results support a model in which HBOT enhances tissue readiness for repair and remodeling, while physiotherapy converts that biological advantage into functional recovery. This combined strategy may represent a promising, evidence-aligned pathway for managing one of the most disabling late effects of pelvic radiotherapy, especially in tertiary survivorship settings such as those in Islamabad.

CONCLUSION

Radiotherapy-induced pelvic fibrosis is a persistent and life-altering consequence of pelvic cancer treatment, often marked by chronic pain, restricted mobility, functional decline, and reduced quality of life. The findings of this randomized controlled trial conducted at a tertiary care hospital in Islamabad provide strong clinical support for a combined treatment strategy using **hyperbaric oxygen therapy (HBOT) alongside structured physiotherapy**. Over the 8-week intervention period, participants receiving HBOT plus physiotherapy demonstrated substantially greater improvements than those receiving physiotherapy alone across all key outcome domains.

Most importantly, the combined treatment group experienced a pronounced reduction in pain intensity, demonstrating that meaningful symptom relief is achievable even in chronic radiation-related injury. Functional outcomes also improved significantly, as evidenced by superior gains in pelvic and hip mobility. Furthermore, the marked reduction in fibrosis severity suggests that this approach does more than reduce symptoms—it may contribute to measurable changes in tissue behavior and pliability. These clinical improvements translated into a clear increase in health-related quality of life, underscoring the value of addressing both the biological and mechanical components of radiation fibrosis.

Taken together, the study reinforces an emerging clinical perspective: **pelvic fibrosis should not be treated as a static end-stage condition**, but rather as a modifiable chronic injury that can respond to targeted regenerative and rehabilitation interventions. Integrating HBOT into pelvic oncology rehabilitation appears to enhance tissue recovery potential, while physiotherapy converts that biological improvement into functional restoration. This combination therefore represents a promising model for improving survivorship outcomes in pelvic cancer patients, particularly in tertiary care settings where late radiotherapy toxicity is frequently encountered.

RECOMMENDATIONS

1. Clinical Practice Recommendations

1. **Adopt multidisciplinary rehabilitation pathways:** Oncology follow-up services should integrate structured pelvic rehabilitation with access to hyperbaric medicine where available. Patients with significant fibrosis-related pain and mobility restriction should be referred early rather than after prolonged symptom progression.
2. **Use HBOT as a targeted adjunct for severe fibrosis:** Based on observed improvements, HBOT should be considered for patients with moderate-to-severe radiotherapy-induced pelvic fibrosis, particularly when conventional physiotherapy yields limited response or when tissue stiffness and hypoxia-related symptoms are prominent.
3. **Standardize assessment in rehabilitation clinics:** Routine survivorship assessments should include pain scoring, ROM measurement, fibrosis grading, and quality-of-life tools such as EQ-5D to enable early identification and follow-up of pelvic fibrosis.
4. **Prioritize patient education and home-based continuation:** Rehabilitation outcomes may improve further when patients continue mobility, stretching, and pelvic floor relaxation programs at home. Structured self-management plans should be emphasized as part of discharge planning.

2. Recommendations for Healthcare Systems (Pakistan / LMIC Context)

1. **Expand survivorship rehabilitation services:** Many patients in Pakistan complete cancer treatment without long-term supportive

care. Establishing survivorship rehabilitation clinics within tertiary oncology centers may reduce disability and improve reintegration into daily life.

2. **Increase HBOT availability and referral pathways:** Hospitals with hyperbaric chambers should develop standardized referral criteria for radiation-induced pelvic injury, ensuring that eligible patients are identified and treated within appropriate timeframes.

3. **Training and capacity building:** Physiotherapists and oncology teams should receive structured training in pelvic oncology rehabilitation, radiation fibrosis management, and trauma-informed care to improve clinical outcomes and patient comfort.

3. Recommendations for Future Research

1. **Long-term follow-up studies:** Future trials should include follow-up periods of at least 6–12 months to determine whether improvements in pain, ROM, fibrosis severity, and QoL are sustained and whether maintenance physiotherapy improves durability.

2. **Larger multi-center trials:** Replication across multiple hospitals in Pakistan and other regions would strengthen generalizability and help develop national clinical guidelines.

3. **Mechanistic and imaging-based evaluation:** Future studies should incorporate objective measures such as ultrasound elastography, MRI fibrosis mapping, or biomarkers of collagen remodeling to verify tissue-level changes beyond clinical scoring.

4. **Cost-effectiveness analysis:** Given that HBOT is resource-intensive, economic studies are needed to determine whether the combined approach reduces long-term healthcare costs by decreasing chronic pain burden, repeated consultations, and disability-related productivity loss.

5. **Subgroup analysis:** Future research should explore whether outcomes differ according to cancer type, radiation dose, time since treatment, baseline fibrosis severity, and age, to refine patient selection criteria.

Final Clinical Message

This study highlights that **HBOT-enhanced physiotherapy is a clinically valuable intervention** for patients living with radiotherapy-induced pelvic fibrosis, producing superior outcomes compared to physiotherapy alone. Implementing this combined strategy within tertiary oncology rehabilitation services may significantly improve survivorship care by reducing pain, restoring movement, decreasing fibrosis severity, and enhancing overall quality of life.

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