Radiation Therapy for Benign Conditions

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to conduct timely, rigorous, and independent systematic reviews to support VA clinicians, program leadership, and policymakers improve the health of Veterans. ESP reviews have been used to develop evidence-informed clinical policies, practice guidelines, and performance measures; to guide implementation of programs and services that improve Veterans' health and wellbeing; and to set the direction of research to close important evidence gaps. Four ESP Centers are located across the US. Centers are led by recognized experts in evidence synthesis, often with roles as practicing VA clinicians. The Coordinating Center, located in Portland, Oregon, manages program operations, ensures methodological consistency and quality of products, engages with stakeholders, and addresses urgent evidence synthesis needs.

Nominations of review topics are solicited several times each year and submitted via the ESP website. Topics are selected based on the availability of relevant evidence and the likelihood that a review on the topic would be feasible and have broad utility across the VA system. If selected, topics are refined with input from Operational Partners (below), ESP staff, and additional subject matter experts. Draft ESP reviews undergo external peer review to ensure they are methodologically sound, unbiased, and include all important evidence on the topic. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. In seeking broad expertise and perspectives during review development, conflicting viewpoints are common and often result in productive scientific discourse that improves the relevance and rigor of the review. The ESP works to balance divergent views and to manage or mitigate potential conflicts of interest.

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Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

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Technical Expert Panel

To ensure robust, scientifically relevant work, the technical expert panel (TEP) guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members included:

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Disclosures

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The findings and conclusions in this document are those of the author(s) who are responsible for its contents and do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. The final research questions, methodology, and/or conclusions may not necessarily represent the views of contributing operational and content experts. No investigators have affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

Executive Summary

KEY FINDINGS

We identified 48 studies on the use of low-dose radiation therapy (RT; <60 Gy) for the treatment of 9 prioritized benign diseases: heterotopic ossification, keloids, plantar fasciitis, pterygium, osteoarthritis, Dupuytren's contracture, Ledderhose disease, Peyronie's disease, and hidradenitis suppurativa.

Heterotopic Ossification (10 Randomized Controlled Trials [RCTs])

- RT may reduce the occurrence of heterotopic ossification. There was no significant difference in function (all with low confidence). Studies provided insufficient evidence (no conclusion) for radiologic failure, side effects, and patient satisfaction, experience of care, or quality of life.

Keloids (4 RCTs and 2 Nonrandomized Comparative Studies [NRCS])

- There was no significant difference in pain after RT (low confidence). Studies provided insufficient evidence (no conclusions) for recurrence of keloids, cosmetic outcomes, skin condition, or side effects and complications. No study reported data on patient satisfaction, experience, or quality of life.

Plantar Fasciitis (5 RCTs)

- RT may improve function. There was no significant difference in plantar fasciitis thickness, a composite measure of pain and function, and side effects (all with low confidence). Studies provided insufficient evidence (no conclusion) for pain or use of secondary treatment. No study reported data on patient satisfaction, experience, or quality of life.

Pterygium (Brachytherapy – 2 RCTs, 2 NRCS, and 1 Single Group Study)

- Studies provided insufficient evidence (no conclusion) for the recurrence of pterygium, symptomatic improvement, cosmetic results, or side effects. No study reported data on patient satisfaction, experience, or quality of life.

Pterygium (Non-Brachytherapy – 1 Single Group Study), Osteoarthritis (2 RCTs, 3 Single Group Studies, and 1 Systematic Review of Single Group Studies), Peyronie's Disease (5 Single Group Studies), Dupuytren's Contracture (5 Single Group Studies), Ledderhose Disease (1 RCT and 3 Single Group Studies), and Hidradenitis Suppurativa (1 Single Group Study)

- Mostly single group studies found disease-related symptoms improved after RT. Side effects were sparsely reported but included skin reactions. Some studies found patients were satisfied with treatment (certainty of evidence not assessed for these diseases and outcomes).

INTRODUCTION

RT targets inflammatory parameters, impedes cell growth, and is frequently used to treat cancer. Low-dose RT has been proposed as a treatment for benign inflammatory and degenerative musculoskeletal diseases, typically when conventional therapy fails. This includes the use of RT for the treatment (or prevention) of heterotopic ossification, keloids after surgical resection, osteoarthritis, and plantar fasciitis.

Benign inflammatory and degenerative musculoskeletal diseases can cause physical limitations and decreased quality of life. Veterans are at increased risk for some benign inflammatory and degenerative

musculoskeletal, orthopedic, and soft tissue conditions due to the physical demands and injuries related to military service. RT is commonly used for the treatment of benign diseases in Germany. Outside of Germany, RT is rarely used to treat benign conditions. The Veterans Affairs (VA) Evidence Synthesis Program (ESP) was asked by the Veterans Health Administration (VHA) National Radiation Oncology Program for an evidence review on radiation treatment for benign conditions. In collaboration with VA partners, we developed the following Key Question (KQ): *What are the benefits and harms of low-dose radiation therapy for the treatment or prevention of benign hyperproliferative and degenerative skin/epithelial, and musculoskeletal disorders such as keloid scars, hidradenitis suppurativa, Dupuytren's contracture, Ledderhose disease, Peyronie's disease, plantar fasciitis, heterotopic ossification, pterygium, or osteoarthritis in adults?*

METHODS

We searched for peer-reviewed articles in Medline (via PubMed), Embase, and ClinicalTrials.gov from inception to April 1, 2023. One included study was identified by the peer reviewers and was published in May 2023. Eligible studies evaluated the effect of low-dose RT for the 9 prioritized benign diseases (heterotopic ossification, keloids, plantar fasciitis, pterygium treated with and without brachytherapy, osteoarthritis, Dupuytren's contracture, Ledderhose disease, Peyronie's disease, and hidradenitis suppurativa). We excluded studies where participants were <18 years of age, where the majority of patients received re-irradiation of the same anatomic site, where brachytherapy (except for pterygium) was used, and where the majority of patients were treated before 1980. We followed a best evidence approach and prioritized comparative studies (*ie,* RT vs no RT) within each condition of interest. RCTs were given priority over NRCS. Single group studies were included when there were fewer than 5 comparative studies within a disease. When only single group studies were available, we reviewed those studies with the largest sample sizes (up to 5 studies per disease based on study budget). Prioritized outcomes included disease-related symptoms, side effects, and patient satisfaction, experience, and quality of life. Where there were at least 3 studies reporting results from sufficiently similar analyses (based on population, interventions, comparators, and outcomes), we conducted meta-analyses using random-effects models. When there were at least 3 comparative studies per disease, we used GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology to determine certainty of evidence. The review protocol was registered in PROSPERO (CRD42023447241).

RESULTS

Forty-eight studies reported on the effectiveness of low-dose RT for the treatment of heterotopic ossification ($N = 10$), keloids ($N = 6$), plantar fasciitis ($N = 5$), pterygium treated with brachytherapy ($N = 5$) and without brachytherapy ($N = 1$), Peyronie's disease ($N = 5$), Dupuytren's contracture ($N = 5$), Ledderhose disease ($N = 4$), hidradenitis suppurativa ($N = 1$), and osteoarthritis. For osteoarthritis, we included 1 systematic review of 7 single group studies and 5 studies identified from the updated search. Across all 48 studies, there was variation in the total dose of RT (in 47 studies range = 0.5 to 40 Gy and in 1 study <5% of patients received up to 70 Gy), sample size (range = 17 to 2,164), and follow-up (range = 1 to 144 months). ES Table shows summary results by disease.

ES Table. Summary of Findings by Disease

Disease; Patients; Design (Studies)	Disease-Related Outcomes	Side Effects	Patient Satisfaction, Experience, QoL
Heterotopic ossification 1,530; RCT (10)	Low evidence for a difference in heterotopic ossification at follow-up (pooled OR = 0.47, 95% CI [0.19, 1.17]). No difference in function (low confidence). Insufficient evidence (no conclusion) for radiologic failure.	Insufficient evidence (no conclusion)	Insufficient evidence (no conclusion)
Keloids 599; RCT (4), NRCS (2)	Insufficient evidence (no conclusion) for a difference in keloid recurrence at follow-up (pooled OR = 1.32, 95% CI [0.40, 4.33]). No difference in pain (low confidence). Insufficient evidence (no conclusion) for cosmetic outcomes and skin conditions.	Insufficient evidence (no conclusion)	No evidence
Plantar fasciitis 1,153; RCT (2), NRCS (1), single group (2)	Function may improve after RT compared to alterative treatment (low confidence). No difference in plantar fasciitis thickness and a composite measure of pain and function (low confidence). Insufficient evidence (no conclusion) for pain, remission, or use of secondary treatment.	No difference (low confidence)	Insufficient evidence (no conclusion)
Pterygium (brachytherapy) 1,492; RCT (2), NRCS (2), single group (1)	Insufficient evidence (no conclusion) for recurrence of pterygium (pooled OR = 0.75, 95% CI [0.30, 1.92]), symptom improvement, cosmetic results.	Insufficient evidence (no conclusion)	No evidence
Pterygium (non-brachytherapy)[a] 65; single group (1)	Reduction in recurrence.	No evidence	No evidence
Osteoarthritis[a] 3662; RCT (2), single group (3), systematic review (1)	No difference in pain, function, stiffness, patient global assessment, composite measure of pain and function, and mental or physical health.	No difference	No difference
Peyronie's disease[a] 415; single group (5)	Symptoms improved after RT.	No long-term side effect; 39% reported erythema	Some satisfaction with sex life after RT. No evidence on patient satisfaction, experience or QoL.
Dupuytren's contracture[a] 653; single group (5)	Symptoms improved after RT.	Skin complications	Most patients were satisfied with RT. No evidence on QoL.
Ledderhose disease[a] 200; RCT (1) and single group (3)	Reduced pain and improved walking performance.	Skin complications and soft tissue fibrosis (mild)	Improved QoL. Most patients were satisfied with RT.
Hidradenitis suppurativa[a] 231; single group (1)	Symptoms improved after RT.	No evidence	No evidence

Notes. [a] Certainty of evidence not assessed.

Abbreviations. QoL=quality of life; RT=radiation therapy.

Heterotopic Ossification

Ten RCTs conducted between 1988 and 2008 (that analyzed 1530 participants) compared low-dose RT to surgery with or without non-steroidal anti-inflammatory drugs (NSAIDs). Three studies were conducted in US, 6 in Germany, and 1 in the Netherlands. Total radiation dose ranged from 5 to 12 Gy. Nine RCTs had medium risk of bias for poor reporting (unclear method of randomization, not reporting allocation concealment, and not reporting blinding). One RCT reported results from a per protocol analysis and excluded a large number of patients from the RT arm, raising concerns of selection bias (*ie*, high risk of bias).

In summary (ES Table), there was a clinical, but not statistically significant, reduction in the occurrence of heterotopic ossification after RT compared to surgery with or without NSAIDs (9 studies). There was no significant difference in function between RT and surgery with or without NSAIDs (3 studies). Studies provided insufficient evidence for radiologic failure, pain, side effects, and patient satisfaction, experience of care, or quality of life (imprecise and inconsistent estimates and methodological limitations).

Keloids

Six comparative studies (4 RCTs and 2 NRCS) conducted between 1991 and 2021 (that analyzed 599 participants) compared low-dose RT to surgery, surgery with 5-fluorouracil or a topical steroid, or a topical steroid alone. Two studies were conducted in the US, 2 in China, 1 in Nigeria, and 1 in Pakistan. Total radiation dose ranged from 7 to 32 Gy. Three RCTs had medium risk of bias (not blinding participants/personnel and not clearly reporting whether outcomes assessors were independent), 1 RCT had high risk (only reporting outcomes for 52% of treated patients), and 2 NRCS reported unadjusted crude analyses (*ie,* high risk of bias).

In summary (ES Table), studies provided insufficient evidence that RT affects the recurrence rate of keloids compared to alternative treatments (6 studies). There was no difference in pain after RT compared to alternative treatments (1 study). Studies provided insufficient evidence for cosmetic outcomes, skin conditions, or side effects and complications. No study reported quality of life, patient satisfaction, or experience of care outcomes.

Plantar Fasciitis

Five studies (2 RCTs, 1 NRCS, and 2 single group) conducted between 2007 and 2020 (that analyzed 1,153 participants) reported on the use of low-dose RT. The RCTs and NRCS compared RT to platelet-rich plasma therapy, palpation-guided steroid injection, or extracorporeal shock wave therapy. Two studies were conducted in Turkey, 1 in India, and 2 in Germany. Total radiation dose was either 3 or 6 Gy. Two RCTs had medium risk of bias (outcome assessor was not blinded or unclear whether outcome assessor was blinded). The NRCS reported unadjusted crude analyses (*ie,* high risk of bias). Single group studies are unable to estimate the effect of RT on outcomes (*ie,* high risk of bias).

In summary (ES Table), function may improve for patients who receive RT (2 studies). There was no significant difference in plantar fasciitis thickness (2 studies), a composite measure of pain and function (1 study), and side effects (4 studies). Studies provided insufficient evidence for effect of RT on pain or use of secondary treatment. No study reported quality of life, patient satisfaction, or experience of care outcomes.

Pterygium (Brachytherapy)

Five studies (2 RCTs, 2 NRCS, and 1 single group) conducted between 1989 and 2009 (that analyzed 1,492 participants) evaluated the use of brachytherapy for the primary treatment or prevention of recurrence of pterygium after excision compared to excision alone, excision with fluorouracil, or excision with mitomycin C. One study was conducted in Brazil, 1 in Israel, 1 in Nigeria, 1 in Turkey, 1 in Japan, and 1 in Germany. In 4 studies, total radiation dose ranged from 10 to 35 Gy. In 1 study, total radiation ranged from 10 to 70 Gy, but we included this study since <4% of patients received >60 Gy. Both RCTs had no methodological concerns. One NRCS only conducted crude analyses (*ie*, high risk of bias) and 1 NRCS only matched for age and sex (*ie,* medium risk of bias). The single group study was unable to estimate the effect of RT on outcomes (*ie,* high risk of bias).

In summary (ES Table), studies provided insufficient evidence for the effect of RT on recurrence of pterygium, symptomatic improvement, cosmetic results, or side effects. No study reported quality of life, patient satisfaction, or experience of care outcomes.

Pterygium (Non-Brachytherapy)

One single group study conducted between 1987 and 2000 (that analyzed 65 participants) evaluated the use of RT (5 to 30 Gy) for the primary treatment or prevention of recurrence of pterygium after excision. The study authors are from Germany, but the specific location of the study was unclear. The single group study had minimal methodological limitations, but the design was unable to estimate the effect of RT on outcomes (*ie,* high risk of bias).

In summary (ES Table), 23.5% of lesions recurred after RT (1 study). No long-term side effects were reported. The study did not report symptoms, cosmetic outcomes, and patient satisfaction, experience, or quality of life. Certainty of evidence was not assessed for these outcomes.

Osteoarthritis

Six studies (2 RCTs, 3 single group, and 1 systematic review of 7 single group studies) conducted between 2004 and 2020 (that analyzed 3,574 participants) reported on low-dose RT for the treatment of osteoarthritis. Three studies were conducted in Germany and 2 in the Netherlands. Total radiation dose ranged from 0.5 to 6 Gy. The RCTs had no methodological weaknesses. The single group studies had minimal methodological limitations, but the study design was unable to estimate the effect of RT on outcomes (*ie,* high risk of bias).

In summary (ES Table), 4 single group studies but not 2 RCTs reported improvements in pain, function, a composite measure, and somatic measure. Side effects including fatigue, local reactions, skin reactions, and nail reactions were comparable between RT and sham RT (2 RCTs). Single group studies, but not the 2 RCTs, reported improvements after RT on a version of the Short Form Health Survey. Certainty of evidence was not assessed for these outcomes.

Peyronie's Disease

Five single group studies conducted between 1982 and 2008 (that analyzed 415 participants) reported on the use of RT for the prevention or primary treatment of Peyronie's disease. Four studies were conducted in Germany and 1 in the Netherlands. Total radiation dose ranged from 12 to 40 Gy. The single group design was unable to determine the effect of RT on outcomes (*ie,* high risk of bias).

In summary (ES Table), single group studies reported improvements or stabilization after RT in deviation/curvature (4 studies), foci quality (1 study), and an undefined measure of symptoms (3 studies), and a reduction in pain (4 studies) and number and size of foci (1 study). Between 36% and 51% of patients were satisfied with their sex life after RT (2 studies). Five studies reported different side effects that ranged from 0% (long-term) to 39% (erythema). Certainty of evidence was not assessed for these outcomes.

Dupuytren's Contracture

Five single group studies conducted between 1982 and 2013 (that analyzed 653 participants) reported on the use of RT for the primary treatment of Dupuytren's contracture. Four studies were conducted in Germany and 1 in Poland. Total radiation dose ranged from 21 to 32 Gy. The single group design was unable to determine the effect of RT on outcomes (*ie,* high risk of bias).

In summary (ES Table), disease stage (3 studies) and nodules and symptoms (4 studies) either stabilized or regressed in most patients after RT. Skin-related complications were the most commonly reported side effect (5 studies). Most patients were satisfied with treatment (2 studies). No study reported quality of life or experience of care outcomes. Certainty of evidence was not assessed for these outcomes.

Ledderhose Disease

Four studies (1 RCT and 3 single group) conducted between 1996 and 2023 (that analyzed 200 participants) reported on the use of RT for treatment of Ledderhose disease. Two studies were conducted in Germany and 2 in the Netherlands. Total radiation dose ranged from 24 to 32 Gy. The RCT had no methodological concerns (*ie,* low risk of bias). The single group design was unable to determine the effect of RT on outcomes (*ie,* high risk of bias).

In summary (ES Table), pain (4 studies), gait or walking speed (3 studies) and quality of life (1 study) improved after RT. Lesions and symptoms stabilized or improved and nodes and strands decreased or remained stable after RT (2 studies). Skin reactions were the most commonly reported side effect (13% to 25%; 4 studies). Most patients were satisfied with their treatment at follow-up (3 studies). Certainty of evidence was not assessed for these outcomes.

Hidradenitis Suppurativa

One single group study conducted between 1979 and 1997 (that analyzed 231 participants) reported on the use of RT for treatment of hidradenitis suppurativa. The study was conducted in Germany. The total radiation dose ranged from 3 to 20 Gy. The single group study was unable able to determine the effect of RT on outcomes (*ie,* high risk of bias).

In summary (ES Table), after RT 78% of patients had a resolution or improvement of symptoms and 39% of patients had resolution of all symptoms. Side effects and patient satisfaction, experience, or quality of life were not reported. Certainty of evidence was not assessed for these outcomes.

DISCUSSION

RT, which is typically used to treat cancer, can also been used to treat benign inflammatory and degenerative musculoskeletal disorders. We identified few comparative studies that evaluated the effect of RT for the treatment of the 9 prioritized diseases. Furthermore, we were only able to evaluate

the certainty of evidence for 4 of the 9 diseases. The effect of RT on clinical outcomes is mixed. RT shows promise for the treatment or prevention of heterotopic ossification and function for people with plantar fasciitis. Low-dose RT may be safe. Local skin reactions were the most commonly reported side effect, but studies did not consistently report adverse events and it was not always clear whether an adverse event was due to RT, co-occurring intervention (*eg,* surgery), or a natural feature of the lesion. Patients and providers are concerned about the risk of radiation-induced malignancies. No study reported cases of radiation-induced malignancies, but studies were not powered (sample sizes were too small) or designed (follow-up time was too short) to detect this rare outcome. Single group studies predominantly informed the synthesis of the majority of diseases. Findings (especially causal inference) from single group studies need to be interpreted with caution because it is challenging to differentiate treatment effect from symptom resolution that could have occurred naturally over the study observation period.

The evidence base on RT for the 9 prioritized diseases has several important limitations. Few comparative studies evaluate the effect of RT. RCTs had independent outcome assessors but did not blind participants or personnel. Three RCTs evaluating RT employed sham RT as a comparison group, which could serve as a model for future studies. There was heterogeneity among studies both within and across diseases. This included variation in radiation dosing, administration of radiation (*ie,* before or after surgery), comparator group (when included), and timing of follow-up assessments. These differences make it challenging to determine the effect of radiation on outcomes. In addition, there was inconsistent reporting of disease characteristics, disease-related outcomes, and side effects. Finally, few studies reported patient quality of life, satisfaction, or experience.

None of the articles focused on a Veteran or military population. Nevertheless, the clinical findings likely translate to the VA population, as the underlying biology of these conditions do not differ by patient population. Patient satisfaction, experience of care, and quality of life are more sensitive to health system features. Only a few studies reported these outcomes (mostly positive findings), but it remains unknown how Veterans would rate their experience. Veterans may or may not receive radiation from 1 of the 41 VHA-operated radiation oncology centers. The location of care (and burden associated with receiving care) could meaningfully impact satisfaction, experience, and quality-related outcomes. RT is typically used after conventional therapy fails and requires a referral from the primary treating provider. For RT to become part of standard care (inside and outside the VA) requires educating referring providers on the benefits and harms of RT. To increase uptake of RT, VA can take the lead on developing a benign disease care pathway. One of the biggest concerns for patients and providers when considering RT is the risk of radiation-induced malignancies. As noted above, few studies reported on this outcome and no study was adequately designed to detect radiation-induced malignancies. There is an opportunity for VA to help fill this gap. VA administrative data combined with efforts from the VA National Radiation Oncology Program (VA-NROP) could be used to develop a registry to monitor radiation-induced malignancies.

Research Gaps/Future Research

There is a need for well-designed, adequately powered comparative studies. RCTs should consider employing sham radiation as the comparison group or other conservative modalities such as steroid injections. Most observational studies used data from medical records, but they did not account for confounding between groups. Future observational studies, including studies of electronic health records, should at minimum conduct causally explicit analyses to counter confounding bias. There is also a need to better understand patient quality of life, experience, and satisfaction, including

treatment-related burden. Finally, and as noted above, there is a need for a registry to collect data on radiation-induced secondary malignancies.

Limitations

This evidence review has several limitations. We employed a best-evidence approach due to the number of prioritized diseases and published studies. Our review included the strongest available evidence (*ie,* comparative designs prioritized over single group studies). Nevertheless, we may have excluded studies with important data on the benefits and harms of RT for benign conditions. There was large variation in studies, and we were unable to investigate potential sources of heterogeneity of treatment effects. Sometimes it was unclear whether an adverse event was a negative consequence of the treatment. We sought to make minimal inference about adverse events and tried to stay true to how data were reported in the literature.

CONCLUSIONS

RT has been explored as a treatment (typically after conventional therapy fails) for a variety of benign diseases. There were few comparative studies on the use of RT for the treatment of the prioritized benign diseases. RT may reduce the occurrence of heterotopic ossification and improve function in plantar fasciitis. There was no significant difference in pain for people with keloids after RT compared to alternative treatments. We have low confidence in these conclusions due to methodological limitations of the studies, imprecision, and inconsistency. One RCT found pain, walking speed, step rate, and quality of life improved in people with Ledderhose disease after RT compared to sham RT (certainty of evidence was not evaluated). There was either insufficient (due to no comparative design, methodological limitations, inconsistent estimates) or no evidence for the effect RT on most other disease-related outcomes, side effects, or patient satisfaction, experience, or quality of life for people with keloids, pterygium, osteoarthritis, Peyronie's disease, Dupuytren's contracture, and hidradenitis suppurativa. Despite the gaps in the evidence, we found no indication that RT should not be used after conventional therapy fails for the 9 prioritized diseases. We assess that there is equipoise about the clinical utility of RT in patients failing conventional therapies. Future research should conduct comparative studies (RCTs or NRCS that control for confounders) for the use of RT for benign conditions.