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Radiotherapy for Hidradenitis Suppurativa: A Systematic Review

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Radiotherapy · X-ray · Hidradenitis suppurativa · Therapy · Radiation

Abstract
Background: Hidradenitis suppurativa (HS) is a chronic inflammatory dermatosis characterized by painful nodules, abscesses, sinus tracts, and scarring mainly in the intertriginous areas. Patients with HS often experience inadequate responses to traditional treatment consisting of lifestyle modification, topical and systemic antibiotics, hormonal modulators, biologics, and procedural modalities. Low-dose radiotherapy has been used in benign cutaneous conditions, including HS; however, there is a paucity of literature summarizing its evidence. Herein, we systematically review the current literature on the efficacy of radiotherapy for patients with HS. ***Summary:*** This systematic review of the published literature reports the patient demographics, treatment regimens, efficacy, and adverse effects of radiotherapy in the treatment of HS. The historic timeline of these publications highlights the changes in management recommendations, introduction of more standardized outcome measures, and enhancements in treatment options. Radiotherapy appears to be an option for patients with treatment-resistant HS or who are poor surgical candidates. However, there remains a paucity of consensus on proper candidate selection, dosing, efficacy, and safety of the short- and long-term effects of radiotherapy.

Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory dermatosis characterized by painful nodules, abscesses, sinus tracts, and scarring mainly in the intertriginous areas. Current widely accepted treatment options for HS include various combinations of lifestyle modifications, topical and systemic antibiotics, hormonal modulators, biologics, and procedural modalities. However, the aforementioned treatments often lead to inadequate response even when used in a combined fashion, especially in moderate and severe HS patients. Additionally, these treatment options may be contraindicated in some patients due to drug interactions, side effects, comorbidities, or poor surgical candidacy.

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Radiation treatment, also known by terms such as radiation therapy, radiotherapy, irradiation, or X-ray therapy, administers high-energy particles or waves to diseased areas resulting in cellular DNA damage and death [1]. For this review we will use the term radiotherapy. The millisievert (mSv) is used to define the average accumulated radiation dose to an individual for 1 year where 1 mSv is the dose produced by 1 mGy of radiation [2]. High-dose (more than 250 mSv) radiotherapy is commonly used in malignant diseases, and low-dose radiotherapy (under 100 mSv) has been used to treat benign inflammatory conditions such as keloids, eczema, and psoriasis due to its anti-inflammatory and immunomodulating effects [3–6].

Nearly a century ago, small reports on radiotherapy for patients with HS were published signaling an interest in exploring this treatment modality. The North American Clinical Management Guidelines for HS currently rank external beam radiotherapy as a grade C recommendation (based on consensus, usual practice, opinion, disease-oriented evidence, or case series) and presents it as an option for patients with treatment-resistant HS who are poor excisional candidates [7, 8]. Currently there is a paucity of literature summarizing evidence regarding the use of radiotherapy in HS. Herein, we systematically review the current literature on the efficacy of radiotherapy for patients with HS.

Methods

In August 2020, a systematic review was conducted by 2 independent authors (S.A. and J.S.) on PubMed and EMBASE for articles from 1950 to 2020. The following search terms were used: ("hidradenitis suppurativa" OR "suppurative hidradenitis" OR "hidradenitis" OR "hidradenitides" OR "acne inversa" OR "velpeau disease" OR "verneuil disease") AND ("radiotherapy" OR "brachytherapies" OR "brachytherapy" OR "electro magnetic" OR "electromagnetic" OR "irradiation" OR "radiation" OR "radio therapies" OR "radio therapy" OR "radio treatment" OR "radio treatments" OR "radiotherapies" OR "radiotherapy" OR "radiotreatment" OR "radiotreatments" OR "roentgen therapies" OR "roentgen therapy" OR "roentgen treatment" OR "roentgen treatments" OR "roentgenotherapies" OR "roentgenotherapy" OR "roentgenotherapy" OR "rontgen therapies" OR "rontgen therapy" OR "rontgen treatment" OR "rontgen treatments" OR "therapeutic radiology" OR "X-ray therapies" OR "X-ray therapy" OR "X-ray treatment" OR "X-ray treatments" OR "xray therapies" OR "xray therapy" OR "xray treatment" OR "xray treatments"). Articles were manually screened based on title, abstract, and full text. For abstract-only publications, the full text article was found when possible. Articles were included if they were in the English language, contained original data (non-review and non-commentary), and the study population consisted of HS patients and radiotherapy for HS was discussed. Reference screening for additional relevant articles was then completed on all included articles. Of note, relevant review articles and commentaries also underwent reference screening but were not included in this review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram was used to track the search schema (Fig. 1). All radiation units were converted to gray (Gy) for direct comparison.

Results

A total of 591 citations were identified from the literature search (Fig. 1). Of these, 9 articles examined radiotherapy in HS and met inclusion criteria. Among the 9 articles reviewed, there was a total of 122 patients in the studies; 105 patients were in studies published before the year 2000 and 17 patients in studies published after 2000. Table 1 summarizes the study design, patient demographics, interventions, prior treatments, treated anatomical sites, results, and reported side effects of the included studies.

The first report of radiotherapy in HS was in 1950. Fifty-four patients (25 male, 29 female, mean age 25 years) with either hyperacute or chronic HS of the axilla were exposed to radiotherapy 3 times a week for 5–10 treatments at a per fraction dose of 1 Gy for hyperacute HS and 1.5–2 Gy for chronic HS. The total radiotherapy dose for both groups was 10–12 Gy. Patients also concomitantly received incisions. Patients with a single abscess responded in an average of 3 treatments and resolution of an affected axilla took an average of 7.8 treatments. All patients responded well to treatments with no recurrences and most pain was gone by 2–3 treatments [9].

Five years later, a case series was published with 45 patients (23 acute, 10 chronic localized, and 12 chronic generalized) who had inadequate responses to prior treatments (various topical applications, bathing additives, systemic antibiotics, incision and drainage, and surgery), and who had undergone radiotherapy of unknown dose and duration. In addition to radiotherapy, a combination of hot compresses and systemic antibiotics were used for the acute cases; patients with chronic localized cases also received an unknown dose of autogenous vaccines and staphylococcus toxoid injections. Treated sites included axilla, groin, and "generalized" regions including the mammary fold, umbilical region, and Montgomery's glands of the areola. Results varied based on the disease course; patients with acute disease had no recurrences, patients with chronic localized disease could expect re-

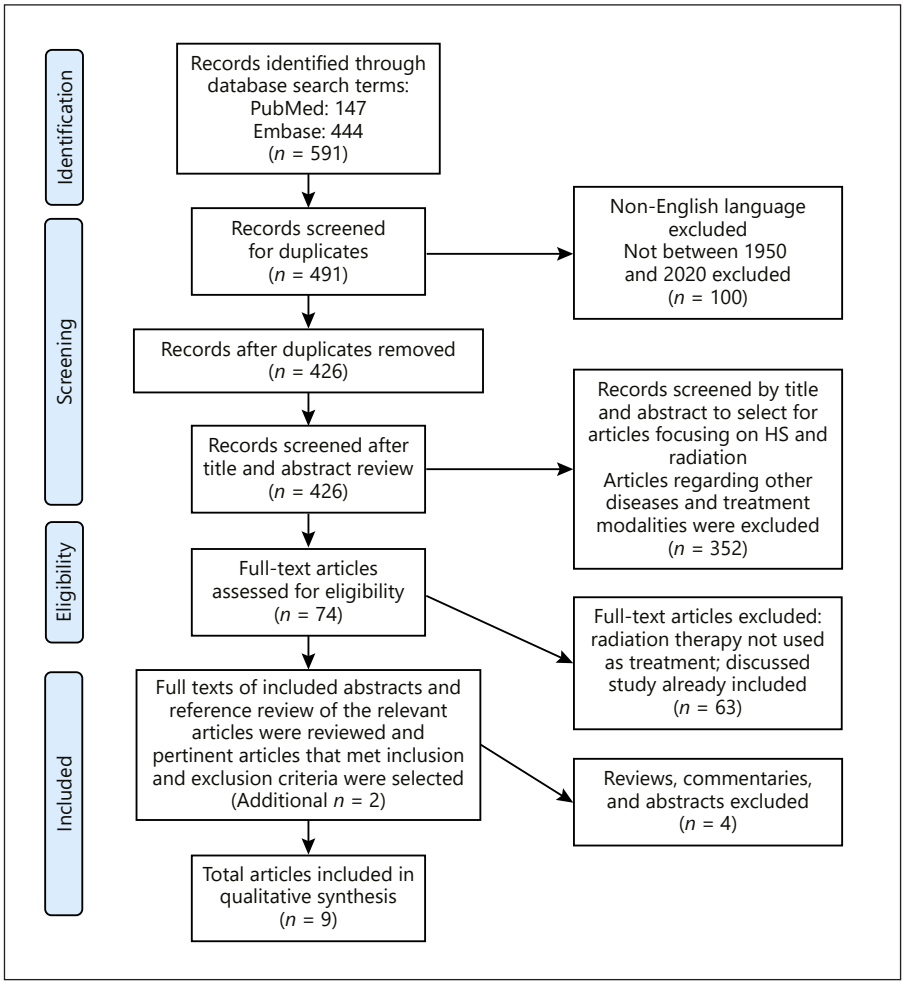

Fig. 1. PRISMA flow diagram (from Moher et al. [24]).

currences, and patients with chronic generalized disease had a uniformly poor response [10].

Beginning in 1965, a single course of radiotherapy at lower doses became the treatment of choice for HS. A case series described 5 patients aged 22–51 years who were exposed to a single course of 4.5 Gy to the affected axilla. Within a few weeks of treatment, most patients only had a few active lesions. There was no mention of supplementary therapy in congruence with radiotherapy. No active lesions in treated sites were reported at follow-up periods ranging from months to years after treatment [11].

After the 1965 case series, there was a halt in publications on HS treated with radiotherapy for nearly 30 years. The reason for this is unknown, however the historical timeline of radiation discoveries and safety in the USA may provide insight. Prior to 1945, radiation safety concerns centered around those with occupational exposures. After the 1945 bombing of Hiroshima, radiation exposure became a public risk. Up until 1959, private organizations were in charge of determining radiation safety standards in the USA. In 1964 the National Committee on Radiation Protection and Measurements (NCRP) was granted a federal charter through the US congress which enacted as Public Law to collect and inform the public on radiation protection, likely provoking concerns of the potential health risk of radiation exposure. From this point in time to the present day, newer, more refined studies on radiation risks and recommendations have been published, likely prompting the resurgence of HS radiotherapy literature [12].

After nearly a 3-decade cessation, literature on this topic reemerged in the mid-1990s, with the majority of the articles published in the 2010s. Radiotherapy was used on axillary HS in a 29-year-old male with AIDS. Several days after a single dose of 4 Gy, the suppuration and pain associated with his HS resolved. Unfortunately, 2 months after treatment the patient died due to unreported causes [13].

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Table 1. Study design, patient demographics, intervention, prior treatments, results, and side effects of the included studies

Reference, year	Study design	Patient demographics	Past treatments	Radiation intervention (per fraction, total dose) and location	Concomitant treatments	Results	Side effects
Schenck [9], 1950	Case series	*n* = 54 (25 male, 29 female) Average age: 24 years (range 15–38) Hurley stage unknown	Most treated with wet compress and I&D, some with chemotherapy (NS)	Hyperacute HS: (1 Gy^1, 10–12 Gy^1) Per fraction dose increased as severity of disease diminishes Chronic HS: (1.5–2 Gy^1, 10–12 Gy^1) Course: 3 times a week for 5–10 treatments Treated location(s): axilla	I&D and dry dressing	Pain mostly resolved after 2–3 treatments Single abscesses responded after an average of 3 treatments An average of 7.8 treatments were given to resolve the axilla All cases responded well with NR	Occasional temporary depilatory effect
Steiner and Grayson [10], 1955	Case series	*n* = 45 23 acute (1 week to 4 months); 10 chronic localized (1–7 years); 12 chronic generalized (1–10 years) Hurley stage unknown	Chronic generalized: systemic antibiotics, autogenous vaccine injections, staphylococcus toxoid injection, injections of hyperpyrexia-producing agents, hormonal treatment, I&D, baths, hot compress with solutions, local irrigations with dilute solutions, topical antibiotics, insulin for diabetics, reducing diets, radical incision with grafting (unknown if these were given prior or in conjunction with x-rays)	Radiation dose not mentioned Treated location(s): axilla, groin, generalized (most or all regions with apocrine sweat glands involved)	Acute: hot compress locally and systemic antibiotics (NS) Chronic localized: antibiotics (NS), autogenous vaccine, staphylococcus toxoid injections	Follow-up timeline unknown Acute: NR Chronic localized: recurrences expected Chronic generalized: uniformly poor response	
Zeligman [11], 1965	Case series	*n* = 5 **Subject A**: 43 years, male Hurley stage unknown	I&D and several oral antibiotics (NS)	(4.5 Gy^1, 4.5 Gy^1) Course: single treatment Treated location(s): axilla		1 month: cystic lesions healed 1 year: NAL 6 years: NR	1 month: defluvium and hyperpigmentation in axilla 1 year: complete regrowth of axillary hair
		Subject B: 28 years, female Hurley stage unknown	Compresses (NS), ointments (NS), I&D, oral erythromycin 250 mg 4 times daily	(4.5 Gy^1, 4.5 Gy^1) Course: single treatment Treated location(s): axilla		3 weeks: few active lesions 3 months: NAL 4 years: NR, NAL	3 weeks: defluvium 3 months: complete regrowth of axillary hair 4 years: atrophic scars
		Subject C: 38 years, female Hurley stage unknown	Penicillin, staphylococcus toxoid injection, tolbutamide, sedatives, oral erythromycin 250 mg 4 times daily	(5 Gy^1, 5 Gy^1) Course: single treatment Treated location(s): axilla		6 weeks: no further lesions 1 year, 7 months: NAL	6 weeks hyperpigmentation and defluvium in axilla 1 year, 7 months: axillary hair had completely regrown, hyperpigmentation
		Subject D: 22 years, female Hurley stage unknown	Tetracycline and I&D	(4.5 Gy^1, 4.5 Gy^1) Course: single treatment Treated location(s): axilla		2 weeks: NAL 4 years and 7 months: NAL	2 weeks: defluvium and faint erythema 2 months, 2 weeks: defluvium and hyperpigmentation 4 years, 7 months: regrowth of axillary hair, residual pigment, and scar formation
		Subject E: 51 years, female Hurley stage unknown	Tetracycline	(4.5 Gy^1, 4.5 Gy^1) Course: single treatment Treated location(s): axilla		1 month: few small lesions 1 month and 3 weeks: active lesions decreased in size 4 months: NAL 9 months: NAL	1 month: defluvium and pigmentation 4 months: axillary hair had regrown and hyperpigmentation 9 months: hyperpigmentation and scarring
Johnson and Forbes [13], 1994	Case Report	*n* = 1 29 years, male with AIDS Hurley stage unknown	PR to local care and antibiotics, physical condition precluded surgical management	(4 Gy^2, 4 Gy^2) Course: single treatment Treated location(s): axilla		Several days: suppuration and pain resolved Last 2 months of life: free of this incapacitating problem	Patient died 2 months later for reasons NS

Table 1 (continued)

Reference, year	Study design	Patient demographics	Past treatments	Radiation intervention (per fraction, total dose) and location	Concomitant treatments	Results	Side effects
Jansen et al. [18], 2005	Applied Science			(Per fraction unknown, 6 Gy)		Effective dose is 16 mSv with the colon, skin, and ovary contributing the most Risk of a fatal tumor in a female is 2 per 1,000 treated Hereditary effects of treatment seem to be acceptable Estimated lifetime risk per 1,000 patients for a fatal tumor: 25 years old: 3 50 years old: 0.8 75 years old: 0.3	
Trombetta et al. [14], 2010	Case report	$n = 1$ 53 years, female Hurley stage unknown	Antibiotics (NS), surgical resection ×2	Round 1: (1.5 Gy^2, 4.5 Gy^2) Course: over 3 days Rounds 2 and 3 (residual lesions): (2 Gy^2, 6 Gy^2) Course: over 3 days Round 3 new lesion: (2.5 Gy^2, 7.5 Gy) Course: over 3 days Treated location(s): inguino-femoral folds, axilla, medial thigh, perineum, groin		3 weeks after round 1: marked improvement 1 month after round 2: clinically resolved 4 months after round 2: 2 new lesions and 2 recurrent lesions 2 weeks after round 3: all lesions resolved 2.75 years after round 3: NR	No acute side effects 2.75 years after round 3: no chronic side effects
Patel [15], 2013	Case series	$n = 5$ Three Hurley stage III, two Hurley stage II Average age: 45 years (range 40–51)	Topical cleansers, and topical or oral antibiotics Surgery (NS), radiation, YAG-laser, infliximab, tretinoin	(2.5 Gy, 7.5 Gy) Course: once daily for 3 days Treated location(s): axilla, perineum, inguinal folds, and intergluteal folds		2 months: no CR but more than 50% of lesions had at least PR Axillae lesions: 100% PR Infragluteal/buttock lesions: 67% PR Groin lesions: 50% PR Perineum lesions: 0% PR	After 2nd round: one patient experienced increased swelling
Garcia-Grande et al. [16], 2013	Case series	$n = 10$ 9 Hurley stage III 1 Hurley stage I Average age: 40 years (age range unknown)	Topical and oral antibiotics, surgery (NS) and infliximab	(4–5 Gy, 20 Gy) Course: daily for 4–5 days Treated location(s): axilla, groin, perineum, perianal and infra/inter-mammary folds		CR was observed in ≥50% of lesions and PR was observed in ≥90% of lesions	
Paul et al. [17], 2016	Case report	$n = 1$ 46 years, male	Benzoyl peroxide wash, pentoxifylline, possibly isotretinoin, fluconazole, griseofulvin, rifampin, minocycline, ciprofloxacin, oral antibiotics, broad-spectrum intravenous antibiotics, adalimumab, infliximab, extensive debridement, intralesional triamcinolone	Groin[3]: (2.5 Gy, 10 Gy) Course: daily for 4 days 5 weeks later, occiput[3]: (2.5 Gy, 10 Gy) Course: daily for 4 days Treated location: groin and occiput		Occiput: substantial local improvement 2 weeks after treatment to groin: substantial improvement in thigh lesions and CR of forearm despite being outside the radiation zone 11 weeks: NR	No acute adverse reactions 11 weeks: no toxic effects

I&D, incision and drainage; NS, not specified by authors; CR, complete response; PR, partial response; NAL, no active lesions; NR, no recurrences.
[1] Converted rad (r) to Gy; 1 r = 0.01 Gy.
[2] Converted cGy to Gy; 100 cGy = 1 Gy.
[3] Brachytherapy: treats a more precise localized zone.

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Prior to 2010, the radiotherapy dose patients received was determined at the beginning of treatment and not adjusted. In 2010 a case report on a 53-year-old female was presented introducing a new radiotherapy time course. This time course incorporated multiple rounds of treatment at various fractions and total doses depending on the stage of the lesion. All rounds of radiotherapy were received over the course of 3 days. During round 1, the patient received a total of 4.5 Gy at 1.5 per fraction. During round 2, the residual lesions were treated at a total dose of 6 Gy at 2 Gy per fraction. This protocol resulted in clinical resolution a month after therapy. Four months later, 2 lesions had recurred and 2 new lesions were present. The recurrent lesions received another round of radiotherapy for a total dose of 6 Gy at 2 Gy per fraction and the new lesions received a total dose of 7.5 Gy at 2.5 Gy per fraction. Two weeks later, all lesions resolved and nearly 3 years later the patient has had no recurrences [14].

In 2013, a case series reported that the response rate of HS lesions to radiotherapy appears to vary based on the anatomical location. Five patients were treated with radiotherapy at 2.5 Gy per fractions once daily for 3 days for a total dose of 7.5 Gy. Two months later, the authors found that at least partial improvement was observed in 100% of the axillae lesions, 67% of the infragluteal/buttocks lesions, and 50% in the groin lesions. No complete responses were observed, and there was a lack of response to radiotherapy in the perineum [15]. A second case series published in 2013 with 10 patients used a higher per fraction dose and total dose (20 Gy at 4–5 Gy) over the course of 2–5 days and found that a complete response was observed in ≥50% of lesions and a partial response was observed in ≥90% of lesions [16].

Most recently in 2016, a 45-year-old man with severe HS was reported to have been treated with a new form of radiotherapy called brachytherapy, which is used to treat a more precise localized zone. The treatment consisted of a total dose of 10 Gy at 2.5 Gy per fraction daily for 4 days to the groin and occiput. Substantial improvement was noted at both anatomical locations. Of note, lesions on the thigh and forearm also resolved despite being outside the treatment zone (abscopal effect). No recurrences were noted at 11 weeks of follow-up [17].

Among all aforementioned studies, patients had tried several other therapies prior to the initiation of radiotherapy. The most common side effects included temporary defluvium (hair loss) at treated sites, erythema, hyperpigmentation, and atrophic scaring.

In 2005, the first risk analysis of radiotherapy was performed to model the risk of fatal tumor development. The treatment framework was designed from a treatment regimen used on a female patient who received a total dose of 6 Gy for HS of the groin. The authors found that the risk of fatal tumor development in a woman was 2 per 1,000 treated, with the most at-risk organs being the colon, skin, and ovary. Of note, lifetime risk of fatal tumor development decreased with increased age at radiotherapy treatment (3 per 1,000 for 25 years of age, 0.8 per 1,000 for 50 years of age, and 0.3 per 1,000 for 75 years of age). Mutagenic effects of radiotherapy to the gametes are relatively low, thus radiation effects to the offspring seem to be acceptable [18].

Discussion

Radiotherapy appears to be a viable option for patients with treatment-resistant HS or who are poor surgical candidates, such as those with disease in inoperable or extensive anatomical locations, and those with specific medical comorbidities. Among the reviewed studies, patients experienced positive results with very minor adverse effects. However, long-term follow-ups were not reported so long-term adverse effects such as secondary malignancy are unknown. In general, chronic radiotherapy can be associated with more serious and permanent adverse cutaneous effects, including textural changes, cutaneous breakdown, fibrosis, poikilodermatous changes, loss of hair follicles and sweat glands, loss of nail appendages, and secondary malignancies (primary squamous cell carcinoma and basal cell carcinoma) [19]. Patients with chronic HS ulcerations have an increased risk of squamous cell carcinoma. However, it is unknown if radiotherapy will increase or decrease this risk. Decreasing the inflammation with appropriate HS treatments may reduce the risk of squamous cell carcinoma but it is possible that exposure to radiation may increase the risk due to the additive effect. Thus, HS patients should be closely monitored for cutaneous malignancy despite achieving disease remission. Quantifying the risk of secondary malignancy in each anatomical site is important in HS patients as the risk may vary by location.

Radiotherapy in HS was cited as a potential treatment option in the mid-1900s and has regained attention in more current literature after a 3-decade break. Currently, a phase I clinical trial (NCT03040804) examining the safety of radiotherapy in the treatment of advanced HS is in the recruitment phase; 5 fractions of 1.5 Gy will be introduced over 1 week for a total dose of 7.5 Gy and patients will be followed for 3 months to observe changes in

quality of life, cutaneous discharge, and immunohistochemistry [20]. Furthermore, radiotherapy has also been used in dissecting cellulitis and may be a therapeutic option for patients with multiple follicular occlusion diseases by targeting multiple anatomic locations [21]. Future research is needed to determine the mechanism of action of radiotherapy in the treatment of HS as well as the optimal dose and duration of use. In addition, larger studies to allow for subgroup analysis of treatment efficacy based on lesion location, lesion type, disease severity, and patient demographics can aid clinicians in choosing optimal candidates for this treatment modality. Finally, long-term safety data is needed, as well as monitoring protocols for cutaneous malignancy at treatment sites. Limitations of the reviewed literature include lack of standard reporting of disease and symptom severity, dynamic disease course, lesion types, and outcome measures, thus creating challenges for comparisons across reports.

Conclusion

Recent literature has highlighted the potential benefits of radiotherapy in HS. Future clinical investigations are needed to guide candidate selection and establish the dosing, efficacy, and safety of short- and long-term effects of radiotherapy. Incorporating newly developed clinical and patient-oriented grading tools can be important for standard interpretation of efficacy [22, 23]. With improved understanding of the aforementioned factors, radiotherapy can be strategically incorporated to complement other medical, procedural, and lifestyle interventions used in HS management, particularly in patients that are poor surgical candidates.

Key Message

Cumulative literature has highlighted the potential benefits of radiotherapy in hidradenitis suppurativa. Radiotherapy may be considered for patients with treatment-resistant hidradenitis suppurativa or those who are poor surgical candidates. Future investigations are needed to determine the optimal radiotherapy regimen and strategies to incorporate it into current management plans.

Conflict of Interest Statement

V.Y.S. is on the board of directors for the Hidradenitis Suppurativa Foundation (HSF), a stock shareholder of Learn Health, and has served as an advisor, investigator and/or speaker for Sanofi Genzyme, Regeneron, AbbVie, Burt's Bees, Dermira, Eli Lilly, Novartis, Pfizer, Galderma, Leo Pharma, SUN Pharma, Menlo Therapeutics, GpSkin, and Skin Actives Scientific. J.L.H. has served as an advisor for Novartis.

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Author Contributions

All authors met the ICMJE criteria for authorship.

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