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Comparative efficacy and safety of energy coagulation in radiation-induced hemorrhagic cystitis: A narrative review

Wei Chern Khern, Retnagowri Rajandram, Novinth Kumar Raja Ram, Shanggar Kuppusamy

Division of Urology, Department of Surgery, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia

To assess the efficacy and safety of using energy devices as treatment for radiation-induced hemorrhagic cystitis (RHC) and to determine the most suitable energy source, settings and techniques based on laser-tissue interaction. A search of Google Scholar, PubMed, and Web of Science databases was conducted uptil February 2024 to identify studies on use of energy devices for RHC. Additionally, ClinicalTrials.gov and the World Health Organization's ICTRP (International Clinical Trials Registry Platform) were searched for ongoing studies. We identified 10 studies fulfilling the search criteria using modalities including Nd:YAG laser, argon plasma coagulation, 980-nm diode laser, and potassium-titanyl-phosphate (KTP) laser. Across studies (n=137), majority (n=116, 84.7%) of RHC patients achieved hematuria resolution after one treatment session, with mean/median hematuria-free intervals of 11 to 16 months. Six patients (4.4%) were unresponsive and underwent cystectomy/urinary diversion. Total adverse events occurred in patients (30/139, 21.6%), including storage symptoms, recurrent hematuria, bladder stones and urinary retention, among others. Typical laser settings involved low power (<40 W), with either a pulse duration of 2–3 seconds or 10–40 milliseconds; some used continuous wave mode. Other standard practises include selective coagulation employed in a "painting" fashion and non-contact mode (3–5 mm). The treatment endpoints were hemostasis, involution of telangiectatic vessels and formation of pale well-circumscribed mucosal ulcer. Energy devices have considerable efficacy and safety to treat RHC patients and can be considered for refractory RHC and as an adjunct after initial management. The various properties of KTP laser confers an advantage over other energy devices.

Keywords: Adverse effects; Cystitis, hemorrhagic; Lasers; Techniques; Treatment outcome

INTRODUCTION

Radiation-induced hemorrhagic cystitis (RHC) results from therapeutic radiation used to treat pelvic malignancies and can lead to significant bladder bleeding. RHC may manifest acutely or chronically, occurring even up to ten years post-irradiation [1,2]. Current practises in the treatment landscape of RHC includes bladder catheterization with intermittent/continuous bladder irrigation, cystoscopy for clot evacuation and confirmation of diagnosis, along with consideration of coagulating pathological areas of the inner bladder wall. Post-cystoscopy, therapeutic instillations such as alum and hyaluronic acid are considered to prevent recurring episodes of RHC. In refractory cases, other treat-

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Corresponding Author: Shanggar Kuppusamy https://orcid.org/0000-0002-2741-3521
Division of Urology, Department of Surgery, Faculty of Medicine, Universiti Malaya, Lembah Pantai, 50603 Kuala Lumpur, Malaysia
TEL: +60-3-7949 2070, E-mail: shanggar@ummc.edu.my

ment modalities may include hyperbaric oxygen therapy, formalin instillation and selective arterial embolization.

Pelvic radiation damages the epithelium, disrupts the protective barrier and increases the risk of bleeding from the radiation-induced obliterative endarteritis [3-6]. Cystoscopy examination typically reveal dilated and friable vessels, indicative of the body's attempt to repair these injuries [7]. The main treatment strategies would be to eradicate these submucosal vessels which are potential bleeding sites. There have been a few case series exploring the treatment of RHC with various energy sources. However, repeated exposure of the bladder urothelium to an energy source after radiotherapy appeared counter-productive and remained a treatment dilemma for clinicians, especially in intractable cases.

This article reviews the current literature on treating RHC using coagulation techniques, with a focus on laser-based approaches due to limited data on other devices like bipolar cautery and argon plasma coagulation (APC). It highlights the effects of various lasers on tissue, offers procedural guidance, and addresses precautions and potential adverse effects to minimize risks. The aim is to assist clinicians in selecting effective coagulating devices and to lay the groundwork for future, more comprehensive trials.

MATERIALS AND METHODS

1. Search strategy

Literature search was performed through three databases (Google Scholar, PubMed, and Web of Science) The search was performed by the primary author using the following search strategies: (cystitis OR radiation cystitis OR hemorrhagic cystitis OR haemorrhagic cystitis) AND (cryoablation OR cryo OR ablation OR diode OR RFA OR radiofrequency OR green OR laser OR electrocautery OR electro OR fulguration OR electrofulguration), and NOT (-interstitial -cystica -glandularis -ectopic -infection). NOT function was limited to title only for Web of Science and Google Scholar. Last search was on February 26, 2024. Also, 2 registers within clinicaltrial.gov and World Health Organization's ICTRP (International Clinical Trials Registry Platform) were searched using keywords of (cystitis OR radiation cystitis OR hemorrhagic cystitis OR haemorrhagic cystitis).

2. Selection criteria

The search yielded a total of 420 studies across three databases. The inclusion criteria were: (1) patients diagnosed with RHC, (2) an energy device was used as treatment, (3) studies that are original with full-text articles available, and (4) articles published in English. Removal of duplicates and screening yielded 15 studies. Of these, a further five were excluded: one study was unretrievable after searches in multiple databases and only appeared by title in a non-peer-reviewed forum [8]; the other four were available only as conference abstracts [9-12]. Ultimately, 10 studies consisting of case series and reports were reviewed. PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) diagram [13] below details the methods described (Fig. 1).

RESULTS

Upon retrieval of the available literature, we analyzed the use of energy modalities for treating RHC to achieve the primary endpoint, defined as the absence of hematuria that would not require subsequent surgical intervention [14]. Our results will be presented in three sections as follows:

1. Efficacy and adverse effects

Different energy modalities were assessed for their effectiveness based on the number of sessions required and the duration that patients remained hematuria-free (Table 1) [6,14-20]. Only eight studies reported the achievement of primary endpoint, with a total of 137 patients. Overall, treating RHC with various energy sources is highly effective, with the majority of patients (n=116, 84.7%) achieving resolution in just one session. Additionally, 15 patients (10.9%) required a second session and another 6 patients (4.4%) had to undergo more invasive procedures like cystectomy or urinary diversion.

Adverse events across the 10 studies with a total of 139 patients were reported (Table 2) [6,14-22]. Treatment-related complications comprised of storage symptoms (n=16, 11.5%), recurrent hematuria needing laser retreatment (n=1, 0.7%) and not needing retreatment (n=5, 3.6%), bladder stones formation (n=2, 1.4%) as well as urinary retention (n=2, 1.4%). Finally, (n=3, 2.2%) experienced adverse effects requiring urinary diversion/ cystectomy and one experienced urethra-scrotal fistula (n=1, 0.7%). The total adverse events were recorded (n=30, 21.6%).

2. Settings and techniques

Our review compiled the varied energy settings and techniques applied for each modality (Tables 3 [15-18,21,22], 4 [6,14,19,20]). With Nd:YAG laser at ≤30 W; 980-nm diode at 50 to 120 W; argon beam coagulator at 30 to 60 W; and potassium-titanyl-phosphate (KTP) laser at 5 to 40 W. Moreover, a variety of pulse durations were utilised; comprising short pulse durations (10–40 milliseconds), some at 2–3 seconds, while others used continuous mode.

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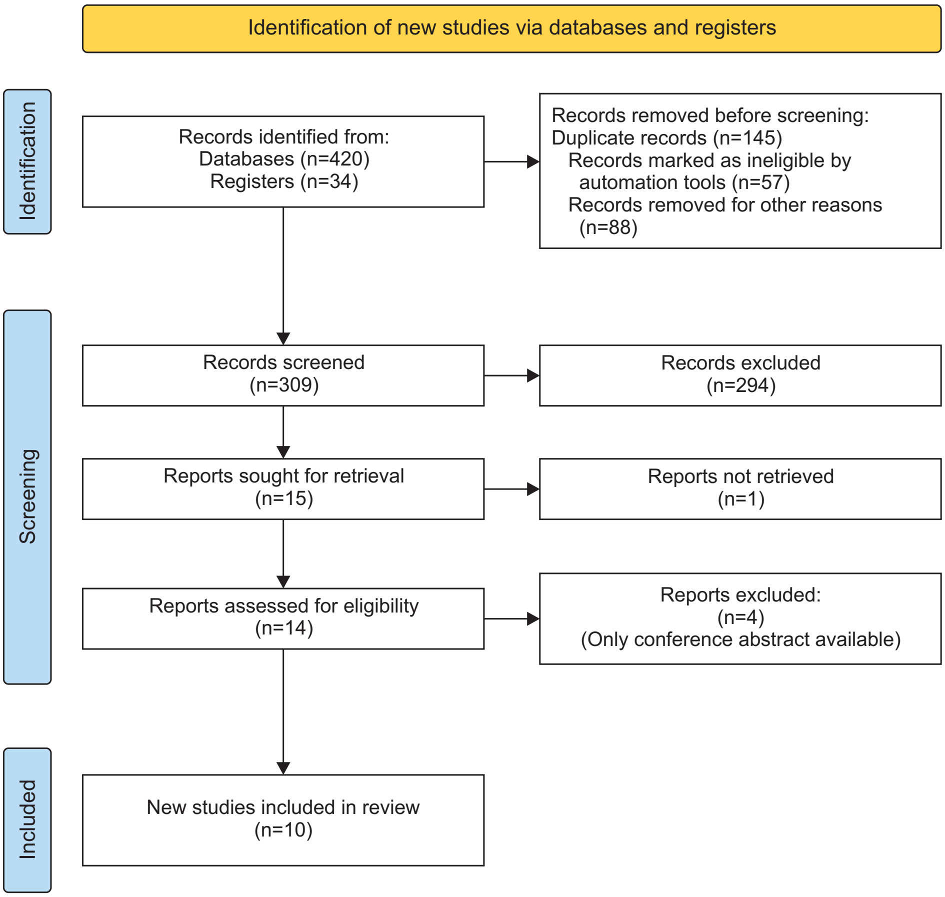

Fig. 1. PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2020 flow diagram [13], summarizing the stages of study selection, from initial identification through databases to final inclusion.

Table 1. Primary endpoint and hematuria-free interval for radiation-induced hemorrhagic cystitis using various coagulation techniques

Study	Modality	Patients resolved in one session (%)	Patients resolved in two or more sessions (%)	Nonresponsive (%)	Mean (range) hematuria-free interval (mo)	Mean (range) follow-up period (mo)
Ravi [15] (1994)	Nd:YAG Laser	39/42 (92.8)	2/42 (4.8)	1/42 (2.4)	NR	14
Kaushik et al. [16] (2012)	980-nm diode laser	4/4 (100.0)	-	-	11 (3–17)	11
Zhang et al. [17] (2021)		16/21 (76.2)	3/21 (14.3), 1/21 (4.76) – three sessions	1/21 (4.8) radical cystectomy after 2 sessions	16 (1–45)	25 (7–48)
Wines and Lynch [18] (2006)	Argon plasma coagulation	6/7 (85.7)	1/7 (14.3)	-	NR	15 (6–36)
Zhu et al. [19] (2013)	GreenLight KTP laser	10/10 (100.0)	-	-	NR	17 (6–36)
Talab et al. [6] (2014)		13/20 (65.0)	4/20 (20.0), 1/20 (5.0) – three sessions 2 out of 5 underwent cystectomy[a]	2/20 (10.0) bilateral percutaneous nephrostomy tubes[b]	11.8 (1–37.1)	-
Martinez et al. [20] (2015)		4/4 (100.0)	-	-	NR	12
Le Bloa et al. [14] (2023)		24/29 (82.7)	3/29 (10.3)	2/29 (6.9) cystectomy	NR	30 (15.0–50.5)
Total (n=137)		116/137 (84.7)	15/137 (10.9)	6/137 (4.4)		

Nd:YAG, neodymium-doped yttrium aluminium garnet; -, no instances; NR, not reported; KTP, potassium-titanyl-phosphate.
[a]:Due to persistent severe urgency and frequency secondary to contracted bladder and extensive cystitis (follow-up discontinued at 5 months and 5.5 months after second session).
[b]:Due to severe hematuria and clot retention despite other multiple treatments (hyperbaric oxygen therapy and cauterization).

Table 2. Adverse effects using energy modalities for radiation-induced hemorrhagic cystitis

Study	Modality	Adverse effects (%)	Common category (n=139)
Lapides [21] (1970)	Electrocoagulation	0/1; No adverse effects.	
Ravi [15] (1994)	Nd:YAG laser	0/42; No adverse effects.	
Zhang et al. [17] (2021)	980-nm diode laser	6/21 (28.6) had frequency and urgency post-procedure. 1/21 (4.8) developed urinary incontinence after second session. 2/21 (9.5) developed bladder stones.	7/21 Storage symptoms 2/21 Bladder stones formation
Kaushik et al. [16] (2012)		1/4 (25.0) underwent urinary diversion due to small capacity bladder.	1/4 Adverse effects requiring urinary diversion/cystectomy
Wines and Lynch [18] (2006)	Argon plasma coagulation	1/7 (14.3) had treatment failure requiring an overnight admission and hematuria resolved spontaneously without catheterization.	1/7 Recurrent hematuria not needing retreatment
Suzuki et al. [22] (2014)		0/1; No adverse effects.	
Zhu et al. [19] (2013)	KTP laser	1/10 (10.0) had recurrence of bleeding 7 months post-treatment; repeat treatment initiated and resolved.	1/10 Recurrent hematuria needing laser retreatment
Talab et al. [6] (2014)		2/20 (10.0) underwent cystectomy due to persistent severe urgency and frequency secondary to contracted bladder and extensive cystitis.	2/20 Adverse effects requiring urinary diversion/cystectomy
Martinez et al. [20] (2015)		1/4 (25.0) experienced urinary retention and mild hematuria recurrence during catheter removal, managed with Foley catheter reinsertion.	1/4 Recurrent hematuria not needing retreatment; 1/4 Urinary retention
Le Bloa et al. [14] (2023)		1/29 (3.4) had acute urinary retention during postoperative catheter removal (catheter placed for 10 more days). 1/29 (3.4) developed a urethra-scrotal fistula (Clavien–Dindo classification grade 3). 9/29 (31.0) had disabling overactive bladder. 3/29 (10.3) had recurrence of hematuria not requiring laser treatment.	1/29 Urinary retention 1/29 Urethra-scrotal fistula 9/29 Storage symptoms 3/29 Recurrent hematuria not needing laser retreatment
Total adverse events (n=139)			30/139 (21.6)

Nd:YAG, neodymium-doped yttrium aluminium garnet; KTP, potassium-titanyl-phosphate.

On the other hand, commonly employed techniques were selective coagulation of actively bleeding and telangiectatic mucosa, in a "painting fashion" 3–5 mm away from the tissue and avoiding quiescent areas in extensive cases.

3. Treatment endpoints

Studies using diode [17] and KTP laser [6] described treatment endpoints as observed visible involution of the telangiectatic vessels, darkening of the vessels through the formation of intravascular thrombus, and discontinuation of blood flow through intravascular endothelial fusion. One study using KTP laser [19] also reported mucosal blanching and immediate hemostasis. On the other hand, studies utilizing APC observed a pale, well-circumscribed ulcer with discrete margins as treatment endpoint [18,22].

DISCUSSION

In our treatment approach for RHC patients, various reviews [3,4,23,24] recommended initial conservative management with saline irrigation. However, when clot evacuation is necessary, cystoscopy should be performed, during which energy coagulation should be considered based on cystoscopy findings (active and potential bleeding areas) after confirming the diagnosis. Additionally, clot burden clearance during cystoscopy is necessary prior to administering intravesical therapy [23].

1. Efficacy and adverse effects across energy devices

Treatment of RHC using various energy modalities has shown potential efficacy, with most patients achieving resolution in just one session and only a small percentage

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Table 3. Summary of various energy settings and techniques for radiation-induced hemorrhagic cystitis

Study	Modality	Energy settings	Techniques applied
Lapides [21] (1970)	Electrocauterization	Minimal coagulative energy	• Active bleeding and telangiectatic areas targeted
Ravi [15] (1994)	Nd:YAG laser	Power ≤30 W Pulse ≤3 s	• "Painting" technique • After gentle clot evacuation, actively bleeding/oozing areas targeted, then areas with small adherent clots or angry-looking • Caution on bladder dome; In diffuse cystitis, only quiescent areas left unattempt
Kaushik et al. [16] (2012), Zhang et al. [17] (2021)	980-nm diode laser	Continuous wave • Kaushik: 50 W: Two patients 120 W: Other two patients • Zhang: 60 W: Telangiectatic friable erythematous mucosa commonly on bladder sidewall; AND 120 W: Conglomeration of submucosal fragile vessels, active bleeding and ulceration commonly in bladder trigone	• Non-contact mode (3–4 mm distance by Zhang) • "Painting" technique and selective vaporization of bleeding vessels by Kaushik
Wines and Lynch [18] (2006), Suzuki et al. [22] (2014)	Argon plasma coagulation	• Wines: Power: 40–60 W Argon flow rate: 1.5 L/min CO_2 insufflation low flow rate: 1 L/min • Suzuki: Power: 30 W Argon flow rate: 0.6 L/min	• Non-contact mode (5 mm distance by Wines) • Targeting bleeding and oozing areas, then possible bleeding areas

Nd:YAG, neodymium-doped yttrium aluminium garnet.

Table 4. Summary of KTP laser settings and techniques for radiation-induced hemorrhagic cystitis

Study	Modality	Laser settings	Techniques applied
Zhu et al. [19] (2013)	KTP laser	Power ≤30 W, pulse duration 10–40 ms	• Noncontact at 3–5 mm away from mucosa • Laser fiber kept at constant motion over the target • First targeted areas of active bleeding and oozing, followed by angry-looking potential bleeding areas • In diffuse involvement, only bleeding or severely congested areas treated • Placed a double J stent before coagulating lesions around ureteral orifices, removed 1-month postoperative
Talab et al. [6] (2014)	KTP laser	Power: 10–40 W	• First targeted areas of active bleeding and oozing, followed by submucosal telangiectatic vessels and conglomeration of fragile vessels • Remove as many potential bleeding sites as possible • In diffuse cases, targeted on lesions more prone to bleeding to reduce procedure time
Martinez et al. [20] (2015)	GreenLight XPS™ with TruCoag™	Power: 10–40 W	• Non-contact mode, 3–4 mm from mucosa • Target active bleeding and prominent telangiectatic vessels as potential source of bleeding • Saline irrigation throughout procedure
Le Bloa et al. [14] (2023)	KTP laser	Coagulation mode at 5 W	• Coagulated entire bladder, suspected higher rates of overactive bladder due to non-selective coagulation and higher energy

KTP, potassium-titanyl-phosphate; GreenLight XPS™, GreenLight Xcelerated Performance System™.

requiring more invasive procedures. In our review, the most common complications were storage symptoms and recurrent hematuria while only a minority had severe adverse effects necessitating urinary diversion or cystectomy. With regards to long-term outcomes, this review found that the use of energy devices for RHC can achieve hematuria-free intervals of nearly a year. Although the Nd:YAG Laser demonstrates the most favourable outcome achieved within a single session [15], the GreenLight KTP laser was more widely studied but showed variable efficacy and adverse events. Meanwhile, the 980-nm diode laser also presents high efficacy but has notable occurrence of adverse events. Although laser therapies emerge as a potentially effective treatment modality, a larger comparative study between energy devices with standardized long-term outcome reporting would yield more reliable findings.

Urgency and frequency are common after treatment with energy device might be linked to the sloughing of coagulated tissue, with bladder stones also suspected for similar reasons [17]. Other potential reasons contributing to higher rates of overactive bladder are non-selective bladder coagulation, higher total energy and longer median surgical time [14].

2. Settings and techniques

We recommend several practices based on our review.

i. Initial steps before coagulation: After carefully inspecting the extent of cystitis and bleeding spots, Trendelenburg position for patients can be considered due to possible bowel adhesions post-radiotherapy [25].

ii. Power settings: Most studies reviewed recommend low power settings, typically ≤40 W to minimize tissue damage and bladder wall perforation risks [15]. Minimal laser energy also avoids the delayed sloughing of coagulated tissue [6].

iii. Pulse durations: Due to the heterogeneity of various pulse durations employed, we are unable to recommend optimal pulse duration mode, hence further research pertaining to this aspect is required. Pulsed waves offer precise targeting with minimal thermal spread due to cooling intervals between pulses, known as thermal relaxation time [26], allowing for selective coagulation of bleeding areas. In contrast, continuous wave mode emits a steady beam effective for achieving uniform coagulation across larger areas [27].

iv. Selective coagulation & techniques: Coagulation should be performed in a "painting" fashion by shifting the laser beam back and forth over the area affected by cystitis, rather than employing a sequence of static impulses. This ensures even energy distribution and avoids excessive heating. It also offers better coagulation depth control to achieve superficial coagulation. Pascoe et al. [12] specified sweep speed of 80 sweeps/min performed at an angle of ~65°. Avoid coagulating adjacent normal tissue and ulcerated areas to prevent perforation [6,19]. Additionally, be cautious when coagulating the bladder dome due to possible adhesion formations with the small bowel from previous radiotherapy [15]. Perform coagulation in a non-contact mode (3–5 mm away from tissue) to reduce tissue damage and allow better visibility. It also ensures eschar formed during coagulation is not pulled away [18]. For lesions around the ureteral orifice, Zhu et al. [19] practised inserting a double J stent and removed it 1 month later. During the procedure, maintain irrigation with a small amount of fluid to conserve bladder thickness and replacing it frequently to provide cooling effect [25].

v. Postoperative outcomes: Operative time should be minimized, ideally within 30–60 minutes [15-17,19,22], and total energy used should be low, with means ranging from 2,171 J to 23,170 J [6,15-17,19] from our review. In addition, minimal bladder catheterization time is recommended to avoid mucosal bleeding due to catheter irritation [6].

3. Recommended type of energy modality

The selection of the ideal laser for treating RHC patients involves factors such as photo-selectivity, penetration, and coagulation depths of lasers. The photo-absorption coefficients of lasers with different wavelengths for water and oxyhemoglobin (Fig. 2) [28] and their tissue penetration depths (Fig. 3) [26] is illustrated, with the KTP laser having the most favourable profile.

KTP lasers (532-nm) are highly selective for hemoglobin and minimally absorbed by water, targeting telangiectatic vessels and sparing the perivascular submucosal tissue and the mucosa above [6]. This minimizes necrosis of surrounding tissue and its sloughing, which may contribute to subsequent bladder stone formation and urinary symptoms [17]. Additionally, the KTP laser, which is far less readily absorbed by water, can effectively transmit through the

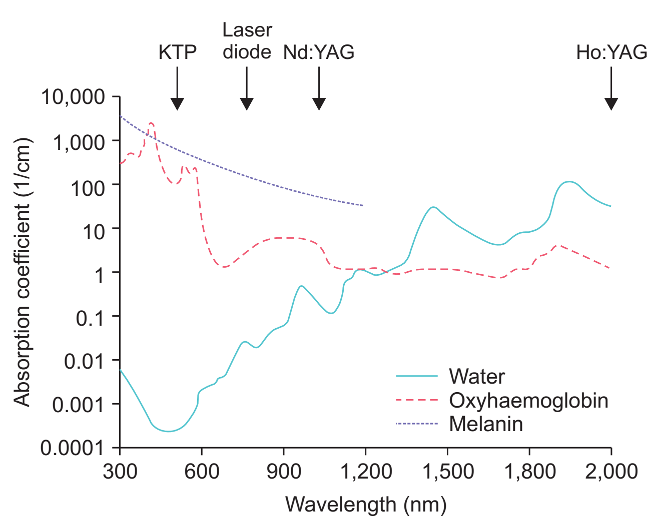

Fig. 2. Photo-absorption coefficient of lasers at different wavelengths. Adapted from the article of Yang et al. [28] (Korean J Urol 2011;52:752-6) under the terms of the Creative Commons Attribution Non-Commercial (CC BY-NC 3.0) license. KTP, potassium-titanyl-phosphate; Nd:YAG, neodymium-doped yttrium aluminium garnet; Ho:YAG, holmium:yttrium-aluminium-garnet.

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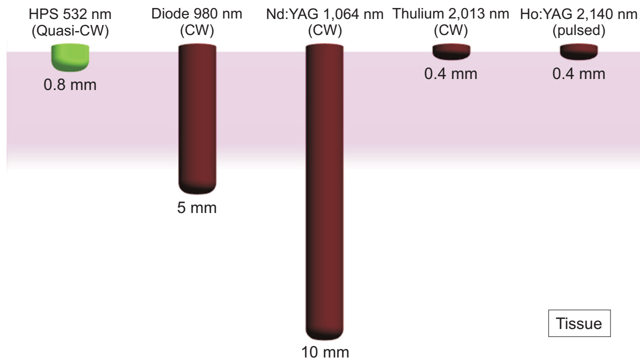

Fig. 3. Laser penetration depths of tissue at different wavelengths. Adapted from the article of Kim and Moon [26] (Korean J Androl 2011;29:101-10) under the terms of the Creative Commons Attribution Non-Commercial (CC BY-NC) license. LBO, lithium triborate; CW, continuous wave; Nd:YAG, neodymium-doped yttrium aluminium garnet; Ho:YAG, holmium:yttrium-aluminium-garnet.

irrigants, minimizing vapor bubbles formed which would otherwise cloud the surgical field as explained by Kim and Moon [26]. In contrast, wavelengths of Nd:YAG (1,064-nm) and diode lasers (980-nm) interact with both water and hemoglobin, causing more extensive thermal injury, leading to larger tissue necrosis areas and increased bladder irritation [6]. As bleeding from RHC originates from mucosal lesions, only superficial, and not transmural coagulation is necessary [15]. While Nd:YAG and diode laser penetrate deeper (10 mm and 5 mm, respectively) [29,30], the KTP laser has a shallow penetration depth of 0.8 mm and coagulation depth of 1–2 mm, making it more suitable for RHC treatment [31].

A study also showed that the KTP laser offers significant advantages, including lower intraoperative complications, reduced length of hospital stays, fewer major events (Clavien grade ≥3), fewer hematuria recurrence and the need for rehospitalization compared to holmium and monopolar electrocoagulation [9]. Therefore, the KTP laser is the recommended mode of coagulation for refractory RHC due to its efficacy and minimal adverse effects [6,19]. Likewise, the newer version of the KTP laser (GreenLight XPS™ with TruCoag™) was proposed to have improved coagulation effect over the standard model [20]. Interestingly, a study introduced the novel 450-nm blue diode laser, demonstrating similar coagulation abilities and photoselectivity to the KTP laser, with added cost-effectiveness and portability, making it a promising area of research [32].

Meanwhile, the argon beam's ability to coagulate relatively superficial layers and wider areas also makes it a safe option [22]. As tissue desiccation leads to increased resistance, the ionized plasma beam shifts to adjacent areas with lower resistance. This process results in a more confined and uniform area of eschar formation [33], and typically produces a coagulation depth of 2–3 mm [34]. Case reports have described success using APC in refractory cyclophosphamide-induced hemorrhagic cystitis [35,36]. Moreover, the low cost and availability of APC, with ease of use and the lack of laser precautions makes it a potential modality [18,22]. Nevertheless, studies using APC are more limited compared to KTP lasers.

4. Addressing limitations and future directions

As our review consists only of retrospective cohort and case studies, a multi-center randomized prospective study comparing newer generations of energy devices would yield more reliable results [37,38]. Similarly, larger studies focusing on bipolar cauterization and APC are needed to better evaluate their efficacy and safety. Given that most patients in this review had previously received multiple treatments, additional data on the initial use of energy coagulation in RHC treatment is needed. Likewise, data regarding the progression and long-term outcome of RHC patients treated with these modalities remains insufficient. Additionally, standardized reporting such as hematuria severity (RTOG/EORTC grades), efficacy, adverse effects, laser settings and procedural techniques would facilitate comparison. One reliable way for reporting the primary outcome is the percentage of patients achieving complete resolution of symptoms at specified time intervals, and not just the absence of hematuria. Factors such as preoperative variables and comorbidities [16-19,39,40], along with surgical techniques and other perioperative parameters [16-19,41] should be detailed and, where possible, correlated with treatment outcomes [42]. Finally, exploring the role of intravesical treatment post-coagulation and multidisciplinary insights into the short- and long-term effects of laser technologies on bladder tissue [32] would provide valuable guidance for future advancements.

CONCLUSIONS

Energy coagulation has considerable efficacy and safety profile to treat RHC patients. It can be considered for refractory RHC and as an adjunct after initial management. The KTP laser has potential advantages due to its photo-selectivity, limited tissue penetration and coagulation depth. Novel energy-based technologies could provide better efficacy and side effect profile that needs to be studied for better management of refractory RHC.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Wei Chern Khern, Retnagowri Rajandram, Novinth Kumar Raja Ram, and Shanggar Kuppusamy. Data acquisition: Wei Chern Khern. Data analysis and interpretation: Wei Chern Khern, Retnagowri Rajandram, Novinth Kumar Raja Ram, and Shanggar Kuppusamy. Drafting of the manuscript: Wei Chern Khern. Critical revision of the manuscript: Wei Chern Khern, Retnagowri Rajandram, Novinth Kumar Raja Ram, and Shanggar Kuppusamy. Administrative, technical, or material support: Retnagowri Rajandram. Supervision: Retnagowri Rajandram, Novinth Kumar Raja Ram, and Shanggar Kuppusamy. Approval of the final manuscript: all authors.

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