

R E V I E W

Oncologic outcome of salvage high-intensity focused ultrasound (HIFU) in radiorecurrent prostate cancer. A systematic review.

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Abstract. *Introduction.* External Beam Radiation Therapy (EBRT) is one of the options available for the treatment of clinically localized prostate cancer. In patients with radiorecurrent localized prostate cancer, Androgen Deprivation Therapy (ADT) is one of the most common therapeutic strategies. However, in the last decades, other salvage treatment options have been investigated, such as brachytherapy, cryoablation and High Intensity Focused Ultrasound (Hifu). *Material and methods.* The oncologic outcome of Hifu in a salvage setting after EBRT failure was investigated. We reviewed the literature from 2005 to 2020 in order to report the oncologic outcome of the technique. *Results.* A total of 1241 patients were analyzed, with a mean age of 68.6 years and a PSA value of 5.87 ng/mL before treatment. Mean follow-up was 24.3 months after treatment, ranging from 3 to 168 months. *Conclusion.* Our review of the literature revealed that salvage Hifu is effective in the treatment of radiorecurrent clinically localized prostate cancer, with an overall survival of 85.2% at 5 years. (www.actabiomedica.it)

Key words: High-Intensity Focused Ultrasound, Hifu, Salvage Hifu, prostate cancer, cancer recurrence, radiotherapy, EBRT, minimally-invasive technique

INTRODUCTION

The chance of having PSA failure after External Beam Radiation Therapy (EBRT) for localized prostate cancer is around 10-30% (1-5). Reportedly, the majority of patients who failed after EBRT receive Androgen Deprivation Therapy (ADT) (6). However, if this is appropriate for metastatic disease, it is palliative in patients with localized recurrence and with more than 5-years life expectancy. Patients with histologically proven prostate cancer recurrence and with no evidence of metastatic disease are eligible for local salvage treatment with a curative intent. Treatment strategies include salvage high intensity

focused ultrasound, salvage cryosurgical ablation and salvage brachytherapy to patients with proven local recurrence within a clinical trial setting or well-designed prospective cohort study (7,8). According with European Urology Association (EAU) and American Urology Association (AUA) Guidelines, radical prostatectomy may also be considered, but in selected cases only.

The aim of our review is to evaluate the safety and cancer control rates of HIFU following failure of EBRT. In addition, we analyzed data in order to find out the preoperative variables able to predict the oncological outcome of salvage HIFU, in an effort to shed more light in patient selection criteria

Materials and Methods

Principles of HIFU

Lynn et al. proposed the focused ultrasound technique in 1942 (9,10), but it was firmly established in the 1950s, thanks to the work by Frank and William Fry, and initially used for ablating brain tissue (11,12). One of the first investigators who conducted trials on this technique applied to human beings was S. Madersbacher (13).

The crucial impetus for the HIFU technique was the development of modern radiological imaging, such as diagnostic ultrasound (US) and magnetic resonance imaging (MRI), which allow non-invasive therapy guidance.

To date, only Hifu treatments of prostate cancer, uterine fibroids and, to some extent, the palliative ablation of bone metastases have found clinical acceptance, while in other pathologies, such as tumors of breast, kidney or liver, the numbers of treated patients remain small.

HIFU uses high-power, highly-focused ultrasound beams that are targeted to converge on a specific point within the body. This technique is also referred to as ultrasonic ablation, sonablation or focal ultrasound surgery. The ultrasound beam causes vibration, thus creating heat (14). An analogy has been made with focusing the sun's rays through a magnifying glass to start a fire (15).

The source of Hifu is a spherical piezoelectric transducer able to produce ultrasonic energy focused on a fixed point. The transducer has the property of changing its thickness in response to an applied voltage, thus creating an acoustic ultrasound wave with a frequency equal to that of the voltage applied. Frequencies used for Hifu therapy cover a 3–4 MHz range. Depending on the ultrasound frequency, site-intensity ranges between 1300 and 2200 W/cm³ (16–18).

The thermal effect relies on the absorption of ultrasound energy by the tissue and its conversion into heat. A temperature of 75°C can be achieved with 1s treatment, well above the level to denature protein (41°C–43°C) and sufficient for coagulative necrosis (19).

The lesions produced by the Hifu technique are elliptical with a volume between 50–300 mm³. They have also been defined as “cigar-shaped” (20).

By combining single lesions, larger target volumes can be ablated without gaps. Between single shots, a pause time is needed in order to prevent tissue boiling and bubble formation, which might distort the US-targeted area.

Focused ultrasound allows a well-circumscribed lesion to be obtained in the focal point without damaging the intervening tissues. The tissue layers outside the ablated area remain unaffected. Since the sharpness of such induced tissue necrosis is comparable to a surgeon's sharp incision, the therapy has also been termed Focused Ultrasound Surgery (FUS) (21). Therefore, this technique provides the advantage of a transrectal treatment with prostate destruction, minimizing the risk of rectal injury (22).

By increasing the intensity of the waves and focusing them on a single point, Hifu allows the deposition of a large amount of energy into the targeted tissue, resulting in its destruction through cellular disruption and coagulative necrosis (23).

Two mechanisms of tissue damage are involved: thermal effect and cavitation (24).

The thermal effect is due to the conversion of ultrasound energy into heat. Tissue damage due to the thermal effect can be classified into three groups: hyperthermia that can destroy malignant cells with low temperatures (41–49 °C) during an extended period (>10 minutes); coagulation, consisting in necrosis of tumor tissue; and vaporization inducing tissue necrosis and charring (temperature >100°C) (25).

Cavitation is the result of the interaction of ultrasound and water microbubbles. This interaction leads to microbubbles vibration and their dissolution within prostate tissue. When the bubbles reach the size of resonance, they suddenly collapse and produce high-pressure shock waves, thus destroying adjacent tissue (26,27). The dynamics of cavitation bubble clouds generated at the tissue boundary in continuous Hifu fields has been experimentally investigated by high-speed photography (28).

The ablation procedure

Hifu is performed through a computerized surgical device equipped with a treatment table, an

ultrasound treatment system connected to an endorectal probe, a safety infrared ray detector, a refrigeration system keeping rectal mucosa below 14°C and a monitor to set and control the treatment procedure through echographic screening. The single piezoelectric crystal alternates between high-energy power for ablation and low-energy for ultrasound imaging (29).

The treatment is performed under spinal anaesthesia. The procedure can be personalized in order to obtain ideal treatment settings: ultrasound frequency, shot duration and waiting time between shots may be modified.

Hifu-induced lesions are visible using standard ultrasound as hyperechoic areas. To date, MRI is considered the gold standard for Hifu efficacy assessment as gadolinium enhanced T1-weighted images can clearly show the necrosis extent (30).

Literature search and selection

We reviewed the literature focusing on side effects and morbidity of HIFU treatment for prostate cancer with the following key words: hifu, salvage hifu, high

intensity focused ultrasound, ultrasonic therapy, transrectal hifu, prostate ablation, focal hifu, radiorecurrent prostate cancer. MedLine and Embase via Ovid database were searched. Selection criteria were: English language, articles published between 2005 and 2020, case series including more than 10 participants and reporting data on oncologic outcome, and case series with at least 12-month follow-up. Articles not reporting the recurrence criterion used by the investigators or based on a recurrence criterion not recommended by the European Association of Urology (EAU) or American Urology Association (AUA) Guidelines, were excluded. All studies that did not meet the inclusion criteria were excluded. In case of studies including overlapping population, only the most recent study was included.

Literature search was conducted from 1st to 12th January 2020. Two Authors (U Maestroni and F Ziglioli) reviewed the articles relevant for potential inclusion independently. When there was not agreement about article inclusion, a third Author (F Dinale) was called to decide for definitive inclusion or exclusion. Literature search and selection is summarized in Figure 1.

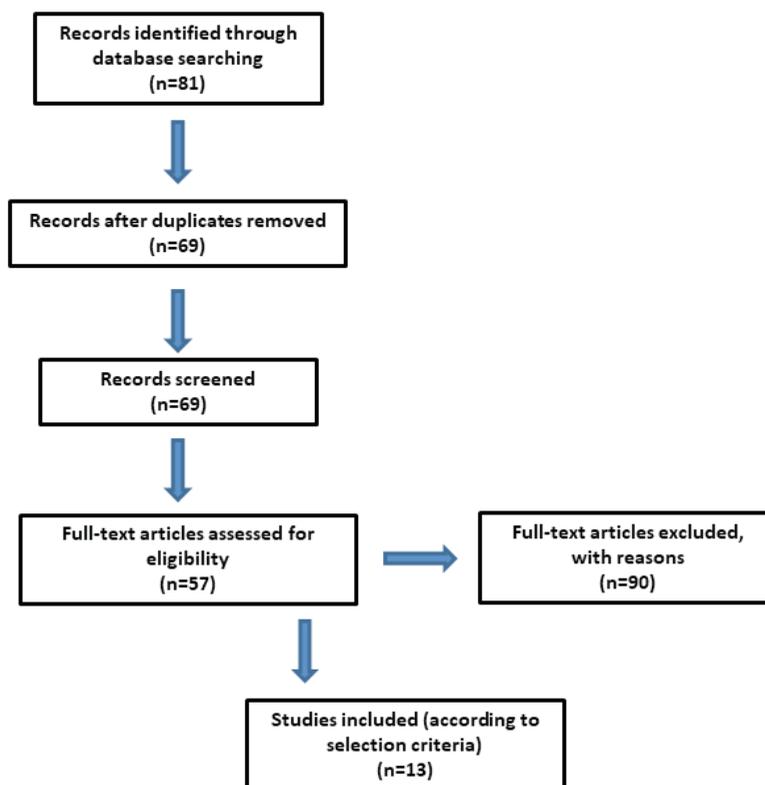


Figure 1.

The methodology of the review is in accordance with the PRISMA criteria (31) and the quality of the review was self-evaluated using the AMSTAR-2 criteria (32). The overall confidence rate in the results of the review is moderate according with the AMSTAR-2 criteria.

Results

After literature search and selection (see Figure 1), demographic and preoperative data are reported in Table 1, while data about the procedure and oncologic outcome, including follow-up, are reported in Table 2. Totally, data from 1241 patients were analyzed. The mean age was 68.6 years, ranging from 53 to 83 years and with a SD of ± 6.11 . The majority of the series reported the pre-EBRT D'Amico risk classification. The low-risk group included 179 patients (18.8%), the intermediate-risk group 337 (35.5%) and the high-risk group 443 (45.6%).

PSA level before salvage treatment ranged from 0 to 62 ng/mL, with a mean value of 5.87 ng/mL and a median of 6.7 ng/mL and a SD of ± 5.52 . The radiotherapy scheme was not reported in all studies. Four studies reported the total radiating dose (mean 67.55 Gy) and 5 reported the dose range. The whole range was 40-78 Gy. The mean prostate volume at the time of treatment was 23.38 mL (SD ± 10.7).

38.3% patients were on androgen-deprivation therapy at the time of salvage Hifu, and 24.71% continued the therapy after the treatment.

In the majority of the series analyzed, the criterion for stating the recurrence was ASTRO/Phoenix. Only in one study the Stuttgart criterion was used.

PSA nadir was 1.1 ng/mL (SD ± 3.39). The time to which PSA nadir was reached was not reported in all series. Limited to these series, PSA nadir was achieved in a mean time of 11.7 weeks (SD ± 9.1). Mean follow-up was 24.3 months after salvage Hifu treatment, ranging from 3 to 168 months.

The overall percentage of patients who had recurrence was 51.6%, independent of the length of follow-up.

Overall survival (OS) was 85.2% at 5 years. Only one study reported a OS of 72% at 7 years.

Discussion

After the advent of PSA, the refinements in the diagnostic technologies, including PSA derivatives and images technologies (33,34), led to an increased number of patients diagnosed with and treated for prostate cancer. Although radical prostatectomy is still considered the gold standard for the treatment of clinically localized prostate cancer, minimally-invasive techniques have become more widespread in the last decades. Among these, high-intensity focused ultrasound has emerged as a valid therapeutic option initially in patients unfit for radical surgery. EAU Guidelines, however, recommend cryotherapy and high-intensity focused ultrasound for localized radiorecurrent prostate cancer within a clinical trial setting or a well-designed prospective cohort study.

The oncologic outcome of this technique has been investigated by many authors (35-39), along with post-operative side effects and Quality of Life (QoL) results (40-43).

According with urologic and oncologic guidelines, EBRT remains the most common approach as an alternative to surgery for clinically localized prostate cancer. However, about 10-15% of patients is reported to develop biochemical failure within 5 years, and up to 60% may experience disease progression (1-5). While in the management of biochemical failure after radical prostatectomy EBRT represents the optimal choice, the most appropriate management for failure after definitive EBRT is still unclear, due to the small number of perspective trials in this setting.

Traditionally, these patients have been treated with Androgen Deprivation Therapy (ADT), generally in the view of a Watchful Waiting (WW) scheme. Salvage radical prostatectomy is limited to patients fit for major surgery and with ≥ 10 years life expectancy.

ADT, however, carries a number of side effects and generally leads to a castrate-resistant state after a median of 2-3 years.

In the literature, 3-10% of patients treated with EBRT with curative intent experience only local failure (44), thus suggesting that local treatment may be effective. This is supported by two recent randomized trials of ADT plus radiation therapy showing that local therapy improves Overall Survival (OS) for patients

Table 1.

	Pt.	Age (y±SD)	Age (range)	Low risk (n,%)	Interm. risk (n,%)	High risk (n,%)	Prior mean PSA (±SD)	Prior PSA median (range)	RT dose (Gy) (±SD)	RT Gy range
Baco E, et al. 2014 [51]	48	68,8 (6)	58-82	10 (21)	12 (25)	20 (42)		16,3 (10,5-24,5)	72,5 (3,3)	64-78
Crouzet S, et al. 2017 [52]	418	68,6 (5,8)		48 (11,5)	77 (18,4)	119 (28,5)	6,8 (7,8)	4,6 (0-62)		
Devos B, et al. 2019 [53]	27	69,9 (6,2)	54-80	4 (14,8)	7 (25,9)	16 (59,3)	4,3 (3,6)	0,2-11,4	70,7 (2,7)	66-78
Gelet A, et al. [54]	71	67 (5,86)		24 (33,8)	13 (18,3)	34 (47,8)	7.73			
Jones TA, et al. 2017 [55]	100	70	53-83	29 (35,8)	40 (49,3)	12 (14,8)	4.9	0,4-14		
Kanthabalan A, et al. 2017 [56]	150	69,8 (6,1)		4 (2,7)	59 (39,3)	62 (41,3)		5,5 (3,6-7,9)	64	
Murat FJ, et al. 2009 [5]	167	68,4 (6,1)		28 (17)	52 (31)	87 (52)	6,89 (7,8)			
Rouvière O, et al. 2013 [57]	46			7 (18,4)	12 (31,5)	19 (0,5)				
Shah TT, et al. 2016 [58]	50	68	64-82					5,9 (2,2-11,3)		50-72,5
Siddiqui KM, et al. 2016 [59]	81	69,4 (6)	57-83	10 (12,3)	30 (37)	41 (50,6)	4,06 (2,88)			
Song W, et al. 2013 [60]	13	68	60-76	4 (33)	5 (41,6)	3 (25)		4.63		
Uddin Ahmed H, et al. 2011 [61]	39	70,5 (6,8)		6 (17,6)	13 (38,2)	15 (44,1)	4.6	3,3 (0,02-27,9)	63	40-74
Zacharakis E, et al. 2008 [62]	31	65	57-80	5 (18,5)	17 (62,9)	5 (18,5)	7.73	0,20-20		66-70
Total	1241			179 (18,8)	337 (35,5)	433 (45,6)				
Mean		68.62	53-83				5.87	6,7 (0-62)	67.6	40-78
Standard deviation		6.11					5.52			

Table 2.

	Device	Whole gland/ Focal (W/F)	Prostate volume (mL) (±SD)	Proced. time (min), SD	PSA nadir (mL) (±SD)	Time to PSA nadir (wks) (±SD)	ASTRO Recurrence criterion	Post sHIFU recurrence	Time of recurrence (mo)	Previous ADT (n,SD)	Post sHIFU ADT	Mean FU (mo)	Median FU (range)	FU range
Baco E, et al. 2014 [51]	Ablatherm	F	21.2	a	0,69 (0,83)	21 (±SD)	ASTRO	16 (33%)	N/R		12 (75%)	16.3		10,5-24,5
Crouzet S, et al. 2017 [52]	Ablatherm	W	20,6 (7,9)		1,9 (5,2)	10,1 (10,7)	Phoenix	213 (51%)	N/R	191 (45,7)	196 (46,9%)	39	39	18-62
Devos B, et al. 2019 [53]	All	W		132,4 (28,6)	1,4 (2,1)		ASTRO/Ph.		N/R	7 su 27			45	2-168
Gelet A, et al. [54]	Ablatherm	W	21,4 (11,1)		1,97 (4,58)	12	Phoenix	35 (49%)	N/R		40 (56%)	14.8		6-86
Jones TA, et al. 2017 [55]	Sonablate	W					Other	30 (30%)	N/R			1.1		0,1-17
Kanthabalan A, et al. 2017 [56]	Sonablate	W			0.67		Phoenix	91 (61%)	N/R	68 (45,3%)		35	35	22-52
Murat FJ, et al. 2009 [5]	Ablatherm	W	18	118	2,38 (6,22)		Phoenix	45 (27%)	N/R	14 (8,4%)	0%	18.1		3-121
Rouvière O, et al. 2013 [57]		W	31 (15)				Phoenix	28 (60,8%)	N/R	15 (32,6%)				48max
Shah T T, et al. 2016 [58]	Sonablate	W			0,12 (0,05-0,83)		Phoenix		N/R	26 (52%)	31 (62%)		64 (49-84)	
Siddiqui KM, et al. 2016 [59]	Sonablate	W	25,5 (8,8)				Phoenix		N/R	19 (22,2%)	21 (26%)	53.5		
Song W, et al. 2013 [60]	Ablatherm	W	25 (median)		0,63 (1,43)	11,2 (7,5)	Stuttgart		N/R				44,5	19-75
Uddin Ahmed H, et al. 2011 [61]	Sonablate	F	26	77	0,57 (0,1-2,3) median	4.3	Phoenix	86 (22,05%)	N/R	29 (74,4)	16 (41%)	17	10-29	
Zacharakis E, et al. 2008 [62]	Ablatherm	W			0.2	12	Phoenix	9 (29%)	N/R	18 (58,06%)			74	3-24
Total														
Mean			23.38	109.13	1.1	11.76		51.60%		38.30%	24.71%			2-168
Standard deviation			10.7		3.39	9.1						24.3		

with locally advanced non metastatic prostate cancer (45,46). For this reason, salvage HIFU may present as an option in local recurrence after definitive EBRT.

In this review, we analyzed the literature on the oncologic outcome and comorbidities of salvage HIFU after prior EBRT. The results show that salvage HIFU provides acceptable oncological control in radiorecurrent localized prostate cancer.

In summary, several of the series analyzed have identified factors associated with good biochemical control after salvage Hifu. Among these, the most relevant were a low pre-salvage PSA and a low risk category at the time of recurrence.

Noteworthy, similar results have been reported for other local techniques, like cryoablation and brachytherapy, thus making it difficult for the physician to candidate the patient to the most appropriate one (47-49). Unfortunately, no algorithm or index is available for predicting the risk of recurrence after these techniques. Only one index is reported in the literature for predicting the risk of recurrence after primary Hifu (50), but to our knowledge it is not widely used, and none is available for salvage Hifu after radiorecurrent prostate cancer.

One of the major consideration in the decision-making process for candidating a patient to a specific salvage therapy, including Hifu, is the toxicity profile, an aspect that may make the difference, at equal safety and effectiveness.

At this regard, we have to say that side effects and toxicities have not been investigated as appropriately as the oncologic outcome. As a matter of fact, toxicities are not standardly reported, and there is no randomized controlled trial comparing salvage HIFU and other local techniques, a weakness that is confusing when a specific treatment has to be chosen. In addition, the variation in the length of follow-up is huge among studies, which makes more difficult to interpret long term results.

The wide differences in side-effects reporting systems among Authors made it challenging to come to a significant result. We may conclude that stress incontinence and urge incontinence, as well as dysuria (including urgency), are the most common reported. If we cannot conclude that these are the most significant after salvage Hifu by the statistical point of view, we can maintain that the most of the attention of physicians

and patients focuses of these side effects, that probably are felt as strictly related to the technique.

It is worth of note, however, that erectile dysfunction is not reported as a side effect by many Authors, although it may have detrimental effects on the quality of life. Even if it is technically evident that impotence can be considered a consequence of Hifu, in many studies we did not find any data about impotence. This lack of data is difficult to interpret, but we may argue that many patients were impotent before salvage Hifu, due to prior EBRT and impotence is conceptually considered more a consequence of radiotherapy than a side effect of salvage Hifu.

Life expectancy is another crucial point when deciding if a patient is eligible for salvage Hifu. As argued by Patekh A et al, men being considered for eligibility should have a long enough life expectancy to gain a reasonable chance to benefit from treatment (47). If life expectancy is less than 5 years, the burden of side effects is too high to make salvage Hifu appropriate as a treatment option, as there is a high probability that this technique would reduce the quality of life without carrying a significant advantage in terms of overall survival. In few words, life expectancy and side effects are two plates of a balance, and both should be weighed carefully for a cautious decision.

This systematic review has some possible limitations. First of all, our analysis is made predominantly on retrospective studies. In addition, many studies we went through are of poor quality, which reduces the number of studies that were considered. Another weak point is the heterogeneity of data collected, that made it difficult to compare the results. The criteria for defining recurrence is not the same through the series considered, and the Stuttgart criterion, even if specific for Hifu, is the less used.

We have already discussed about side effects reporting systems, that were very different among authors, thus making it challenging to come to a significant conclusion. This certainly is another limitation of our analysis.

In conclusion, from the data analyzed it can be stated that salvage Hifu may have potential as a treatment option in radiorecurrent prostate cancer and its effectiveness in cancer control is higher in selected groups of patients, as low- and intermediate-risk and in patients with a low pre-salvage PSA.

Supposing that it may be considered feasible by the ethical point of view, a randomized controlled trial comparing focal treatment modalities would add more value to the current data, as it would improve the approach to radiorecurrent prostate cancer, by selecting patients to be treated with the most appropriate technique.

Conclusion

The advent of PSA and its derivatives, as well as the refinements in the radiologic techniques have increased the detection rate of prostate cancer, thus leading to a higher number of patients treated and a higher number of recurrent cancers.

If Androgen Deprivation Therapy (ADT) is recommended as an option for prostate cancer recurrence after External Beam Radiation Therapy (EBRT), other techniques have emerged in the last decades. Among these, High Intensity Focused Ultrasound (Hifu) may be used within a clinical trial setting or a well-designed prospective cohort study.

Our systematic review aims to provide more insight on the oncologic outcome on salvage Hifu, in the context of the heterogeneity of the studies reported in the literature. In conclusion, data collected across our review revealed that salvage Hifu is effective in the management of radiorecurrent clinically localized prostate cancer. Our study, however, highlighted the lack of robust data on this technique in a salvage setting and we may also conclude arguing that large, multicentric, well designed trials are advisable.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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