High Intensity Focused Ultrasound for Prostate Cancer: Clinical Results and Technological Evolution

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Prostate cancer is responsible for 9% of cancer related death in European men (Black et al 1997) and it is estimated that each year there will be approximately 85,000 new cases of prostate cancer diagnosed in the European Union (Jensen et al 1990).

Strategies for managing prostate cancer include deferred treatment (watchful waiting), radical prostatectomy, definitive radiation therapy and hormone therapy. Deferred treatment is utilized in patients who are expected to die of causes other than prostate cancer based on the age and health of the patient and the characteristics of their disease. Hormone therapy can delay but not stop the progression of prostate cancer and is used when the cancer has spread beyond the prostate. Definitive local therapy is employed when the disease is thought to be clinically localized and has the potential of decreasing the life of patient.

There currently exists no agreement as to the ideal therapy for localized prostate cancer. Radical prostatectomy is the ideal therapy insofar as cancer control is concerned for truly localized prostate cancer. However, it is associated with significant morbidities and quality of life impact and there is no guarantee that the cancer really is completely contained within the prostate. This risk versus reward balance is unacceptable to many physicians and patients and has motivated the development of several minimally invasive therapies including brachytherapy, cryoablation and high intensity focused ultrasound (HIFU).

From the prospective of both the physician and patient the goals of a minimally invasive prostate cancer therapy are to eradicate the local disease, reduce post-operative morbidities, shorten hospital stay and quicken return to daily functions and work. They may also result in a reduction in the overall cost of treating a patient with prostate cancer. Although some of these therapies are relatively new, they are gaining popularity rather quickly and several worldwide experiences have demonstrated that may be able to achieve some or all of these goals.

Brachytherapy is associated with a very short recovery time and little post-operative morbidity. However, as some patient series mature late, onset morbidities are being observed, specifically erectile dysfunction (Raina et al 2003) and full gland cryoablation is associated with high impotence rates (Bahn et al 2002).

Among the novel prostate cancer therapies, HIFU (unique as it is), is in fact non-invasive rather than minimally invasive. It involves no incision. HIFU works by focusing and depositing a large pulse of high-energy ultrasonic waves on a single location. This increases the temperature to a point where the lipids in the cell membrane melt and proteins denature. A reproducible but small volume of ablation is created. Treatment is accomplished by systematically pulsing energy throughout the target volume at different locations until the entire tumor has been ablated. HIFU is a relatively new treatment option that has been investigated at several centers throughout the world, mainly in Europe. This article reviews and compares the published outcomes of HIFU to other prostate cancer therapies. Also, the state of the evolving HIFU technology will be assessed.

HIFU as a therapy for prostate cancer.

When a patient decides on a prostate therapy in concert with his physician several factors are considered principally, efficacy and morbidity. Establishing the efficacy of a novel therapy in relation to established therapies for prostate cancer is an exceedingly difficult task. First off, there exist no prospective, randomized, clinical trials, which compare a novel therapy to an established prostate cancer therapy. As such, one is relegated to comparing published and presented reports of similar groups of patients treated with different therapies. Although such a comparison is inherently flawed due to inevitable variability in patient population, follow-up length, definitions of biochemical disease free survival it does have merit and trends do usually emerge (Katz and Rewcastle, 2003).

Prostate cancer is a slow growing disease and five-year outcomes are generally considered minimally sufficient to definitively evaluate the efficacy of a novel therapy. There exist two such reports for HIFU. In a study of 137 stage T1-T2 patients with a mean PSA of 8.8 ng/ml Gelet et al (2003) found a negative biopsy rate of 81% and 70.1% of patients maintained no biochemical evidence of prostate caner, using the ASTRO definition of biochemical failure (3 successive rises in PSA). Blana et al (2004) treated 146 T1-2, N0, M0 patients with a mean PSA of 7.6 ng/ml and observed a disease free rate (negative biopsy and PSA < 0.4 ng/ml) of 71.5% and a negative biopsy rate of 93.4%. These results are encouraging. For comparative purposes the patient population is as described by Gelet et al could be considered to be between low and moderate risk using the standard definitions of D'Amico (i.e., D'Amico et al 2003). Table 1, modified from Katz and Rewcastle (2003), compares the 5-year biochemical disease free survival rates

as published since 1992 for radical prostatectomy, cryoablation, brachytherapy, 3-dimensional radiation therapy (3D-CRT) and external beam radiation therapy (XRT) with that published by Gelet et al (2003). Given the patient population, the five-year HIFU results compare favorably to all of these established therapies. It is noteworthy that the results of this patient series can be considered to be a 'worst case scenario' as the series includes the first patients ever to undergo HIFU as a therapy for prostate cancer. Further, many of the patients were treated with the original prototype HIFU. Subsequent reports will likely show an improved biochemical control, as proportionally more, or all, patients will have received standardized therapy with a technologically advanced HIFU device.

For in-situ ablations, biopsy provides an excellent surrogate interim therapy evaluation tool. The goal of in-situ ablations is to completely destroy a targeted tissue, in this case the prostate. If successful, subsequent biopsy should show no evidence of disease. Table 2 summarizes studies published in the last 10 years that report negative biopsy rates following brachytherapy, 3-D CRT, XRT, cryoablation and HIFU. To aid in visualization, this analysis is also presented in Figure 1. This figure is, perhaps, the most compelling case for HIFU. The ability of HIFU to locally control prostate appears to be similar if not superior to that of cryoablation, which consistently results in higher negative biopsy rates than any form of radiation therapy.

The other fundamental consideration in assessing a prostate cancer therapy is the morbidity associated with the procedure. Prostate cancer therapy is associated with urinary, rectal and sexual morbidities. Unfortunately, as with efficacy measurement, there is no consistency as to how morbidities are reported. In an attempt to be as fair and complete as possible the literature was surveyed since 1992 and summarized. Table 3

reports the rage of morbidities that have been published following radical prostatectomy, radiation therapy (regardless of delivery method), cryoablation and HIFU.

Impotence is a complicated matter. For all therapies there exists a relatively large range in the reported impotence rates following therapy. The lower end of the reported impotency rate for HIFU is 28%. Although this will need to be substantiated, it is not surprising as there is great accuracy to the geometric volume of HIFU injury that is created. Stopping the therapy abruptly at the lateral margins of the prostate may allow for treatment of only the entire prostate without ablating one or both neurovascular bundles. Any uncompromised neurovascular bundles will be completely untouched and undisturbed during the procedure. This is not possible with most other therapies in which the entire prostate is destroyed. There is manipulation during radical prostatectomy as the nerves are dissected off the prostate and interaction with scattered radiation during. The incontinence rate for HIFU appears to be lower than that of radical prostatectomy but higher than other minimally invasive therapies. This may be due to several factors including the short-term follow-up of most HIFU reports. Incontinence improves with time following prostate cancer intervention. As these data sets mature, it is expected that the incontinence rates will decrease. Rectal injury following HIFU appears to be fundamentally different in nature to that of radical prostatectomy and radiation and more akin to cryoablation. Relatively large minor rectal injury rates are observed following the former two traditional therapies occur with little or no occurrence of rectal fistula formation. First generation technical limitations of both cryoablation and HIFU resulted in initial high fistula rates but they are no longer observed in modern series. Cryoablation, during its first technological iteration was associated with significant rectal fistula

formation but this rate has now dropped to < 0.5% in modern series. The fistula formation rate following HIFU has been reported from 0.5-5% with modern series consistently reporting on the low end of this range. For example, Uchida et al (2004) report a rectal injury rate using the Sonablate®500 of < 0.5%. It is expected that this low fistula rate will be further substantiated in the near future in peer-reviewed publications from multiple institutions.

In summary, there appears to be at least equivalence between the outcomes of standard therapies and those of HIFU. Specifically the results of Gelet et al (2003) and Blana et al (2004) are very encouraging and, for reasons already explained, they should represent the worst HIFU results. Subsequent publications by Gelet and others are expected to should show an improved efficacy further substantiating the role of HIFU. Regarding morbidity, the initial results yield no cause for concern when comparing to other therapies and improvements in technology in concert with procedural standardization should reduce the relatively mild morbidity profile currently observed following HIFU.

Comparison of HIFU technologies

The first commercially available HIFU machine was the Ablatherm® (Edap-Technomed, Lion, France). This is the unit used in the majority of published studies. It utilizes a single 4.0 cm focal length and HIFU crystal to deliver the therapy. Subsequently, Focus Surgery (Indianapolis, IN, USA) developed a second-generation system called the Sonablate 500® that has incorporated several technical advances including a combined therapy / imaging transducer as well as the ability to use multiple focal lengths to increase the resolution of the treatment plan and the quality of the therapy. Initial results with the

Sonablate 500® are encouraging in comparison of those reported on with the Ablatherm®.

Preliminary results of HIFU for prostate cancer have measured efficacy in a relatively consistent manner. Both local control (negative biopsies) and PSA nadir measurements (less than 0.5 and 1.0 ng/ml) have been utilized as well as a combination of local control and PSA nadir < 4.0. Table 4 summarizes the patient demographics and results from results from 12 publications and presentations on HIFU. Figure 2 summarizes this data in a simple to understand form. The results observed when patients were treated with the Sonablate 500® device appear superior to those obtained using the Ablatherm® when one investigates the negative biopsy rates, PSA nadir < 1.0 and PSA nadir combined with negative biopsy. The PSA nadir < 0.5 ng/ml rates observed with the Sonablate (64-65%) fall in the middle of the range observed with the Ablatherm® (55-79%) suggesting equivalence. Table 5 summarizes the differences in morbidity rates observed with the two different devices. The impotence rate of 28-30% associated with the Sonablate 500® is lower than any achieved with the Ablatherm® (45-100%). The incontinence rate of 0-2% is low in comparison to the range observed when using the Ablatherm® (1-23%). Rectal injury appears to no longer be a significant concern for HIFU. Although early series reported fistula rates as high as 5%, series using the newest technology have observed rates <0.5% for the Sonablate 500® and <0.7% for the Ablatherm®. This vast improvement is due to technical advancements. Overall the morbidity profile produced by the Sonablate appears to be superior to that found following treatment with the Ablatherm®.

One study was excluded from the comparison as it used the ASTRO definition of biochemical disease free status. It would have been appropriate to compare to other reports, all of which use PSA thresholds as definitions of biochemical failure. Uchida et al (2004) followed 85 patients for at least one year and observed that 97, 75, 33 and 0% of patients with a pre-HIFU PSA < 10, 10-20, 20-30 and >30 ng/ml, respectfully remained with no biochemical evidence of recurrence.

Although the experience with the Sonablate 500® is relatively embryonic the efficacy results are compelling with negative biopsy rates ranging form 95-100% and nadir rates equivalent or superior to those achieved with the Ablatherm® device. Further, the morbidity profile of the Sonablate 500® appears to be less severe than that associated with the Ablatherm®. This is, in fact, not surprising due to the technological advancements of the Sonablate 500®. Integrating the imaging and therapy devices to the same unit should eliminate potential inaccuracies of anatomical reference that may result during the removal of the imaging crystal and transrectal insertion of the ablation transducer. There exists no way with the Ablatherm® to verify anatomical reference points prior to treatment. Also, the use of multiple focal lengths during treatment represents a significant technological advantage of the Sonablate 500® device. This allows for an ablation zone to be created that more accurately approximates the prostate anatomy. Combined with the use of true 3-dimensional ultrasound images for the treatment planning process rather than a composite of 2-dimensional images to recreate a three dimensional image should yield a more accurate treatment plan. In concert, these technical advances should yield a better treatment with higher efficacy and lower

morbidity. This in fact appears to be the case based upon review of initial results contained in this paper.

Conclusion

The ideal measure of efficacy of a prostate cancer therapy is cancer specific survival. Unfortunately, the follow-up to generate such results is on the order of 20 to 25 years. The urologic community has accepted short-term surrogate markers such as biochemical survival and biopsy results as sufficiently accurate predictors of long-term results. Those observed when HIFU technology is utilized to treat prostate cancer are encouraging at the very least and are associated with a more than acceptable morbidity profile. Research is ongoing and as more and more patients undergo this therapy it is expected that the results will improve solidifying the role of HIFU as a preferred therapy for clinically localized prostate cancer.

Table 1: Efficacy comparison published 5-year biochemical disease free rate following radical prostatectomy (RP), cryoablation (CRYO), Brachytherapy (Brachy), 3-D conformal radiation therapy (3D-CRT), external beam radiation therapy (XRT) and HIFU

	RP	CRYO	Brachy	3D-CRT	XRT	HIFU
Low	76-98%	60-92%	78-89%	76-87%	81-86%	70.1-71.4%
Moderate	60-76%	61-89%	66-82%	51-58%	26-60%	

Table 2: Negative biopsy results observed following radiation therapy, cryoablation and HIFU

Study	Tx	n	Pretreatment PSA (ng/ml)	Gleason	Clinical T Stage	Median follow-up	% negative biopsy
Stock et al. 1996	Brachy	97	75% < 20	82% < 7	T1-T2	18 mos	74%
Ragde et al. 1997	Brachy	126	78.7% < 10; median 5.0	2-6	T1-T2	7 yrs	80%[b]
Ragde et al. 1998	Brachy	152	Median 11.0	91% < 8	98% < T3	10 yr	85%
Zelefsky et al. 1998	3D-CRT	743	Median 15	81< 8	T1-T3	> 30 mos	52%
Dinges et al. 1998	XRT	82	Median 14.0		T2-T3	24 mos	73%
Crook et al. 1998	XRT	102			T1-T3	40 mos	67%[a]
Babaian et al. 1995	XRT	31	70% > 10		T1-T3	51 mos	29%
Laverdiere et al 1997	XRT	120	Median 11.2	24.3% >6	T1-T3	24 mos	38%
Ljung et al. 1995	XRT	55		35% > 6	T1-T3	6.8 yrs	33%
Long et al. 2001	CRYO	975	33% > 10	14.4% 2-5 74% 6-7	75% < T3	2 yrs	82%
Bahn et al. 2002	CRYO	590	24.5% > 10	58.4% >6	T1-T4	5.72 yrs	87%
Donnelly et al. 2002	CRYO	76	38 % > 10	56 % > 6	T1-T3	5.1 yrs	85%
Gelet et al. 2001	HIFU	102	Mean 8.38		T1-T2	19 mos	75%
Gelet et al. 2003	HIFU	137	Mean 8.8		T1-T2	33 mos	81%
Turloff et al. 2003	HIFU	402	Mean 10.9	13% 2-4 77.5% 5-7	T1-T2	22 mos	87.2%
Blana et al. 2004	HIFU	146	Mean 7.6	5 ± 1.2	T1-T2, N0,M0	22 mos	93.4%
Uchida et al. 2002	HIFU	33	Mean 10.97	29% 2-4 66% 5-7	T1b-T2	13.2 mos	100%
Uchida et al. 2004	HIFU	214	Mean 16.1	21% 2-4 71% 5-7 8% 8-10	T1c-T2b	20.6 mos	95%

3D-CRT, three-dimensional conformal radiation therapy; brachy, brachytherapy; TCAP, targeted cryoablation of the prostate; XRT, external beam radiation therapy

a 15% indeterminate

b 13% indeterminate

Table 3. Morbidities observed following radical prostatectomy, radiation therapy, cryoablation and HIFU

	Impotence	Incontinence (any pt, any pad)	Rectal injury			
			Urgency	Bleeding	Diarrhea	Fistula
Prostatectomy	51-96%	7-52%	6-16%	1-3%	6-19%	
Radiation	50-61%	0-15%	19-17%	13-17%	12-42%	
Cryo	82-100%	1.3-5.4%				<0.5%
HIFU	28-100%	0-23%				< 0.5 – 7.5%

Table 4. Comparison of short term efficacy measurement of the efficacy of HIFU using the Ablatherm® device (A) and the Sonablate 500® (S)

Study	Device	n	PSA (average)	Gleason	TMN	f/u mths	PSA nadir		PSA < 4 & neg Biopsy
							< 0.5	< 1.0	
Chaussy 01	A	184	12		T1-T2Nx		61%		
Uchida 02	S	20			T1b-T2b	13.5	65%	90%	100%
Gelet 01	A	102	8.38		T1-T2	19			66%
Gelet 00	A	82	8.11		T1-T2	17.6		56%	92%
Gelet 99	A	50	9.61		T1-T2	14			56%
Beerlag 02	A	111			T1-3NxM0	12	55%		60%
Conit 03	A	118	7.61		T1b-T2c	6	79%		
Gelet 03	A	137	8.8		T1-T2	33	73%	85%	
Gelet 01A	A	20	10.6	30% < 8		9	60%		
Chaussy 00	A	184				3yr	61%		
Blana 04	A	146	7.6	5 ± 1.2	T1-2,N0,M0	22	83%	92%	
Kiel 00	A	62	7.04		T1-T3	27			67.8%
Uchida 02	S	33	10.97	27% 2-4 66% 5-7	T1b-2N0M0	13.2	64%	88%	

Table 5. Comparison of the morbidities observed following treatment with the Ablatherm compared to those observed following treatment with the Sonablate

	Impotence	Incontinence	Rectal fistula
Ablatherm ®	45-100%	1-23%	<0.7-5%
Sonablate 500®	28-30%	0-2%	<0.5-5%

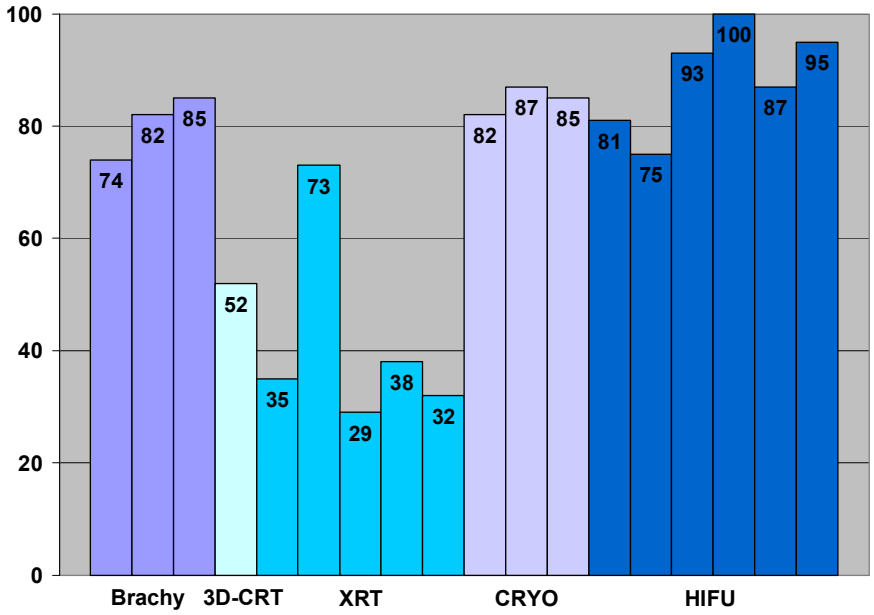

Figure 1. Comparison of negative biopsy results of brachytherapy (Brachy), 3-dimensional conformal radiation therapy (3D-CRT), external beam radiation therapy (XRT), cryoablation (CRYO) and HIFU.

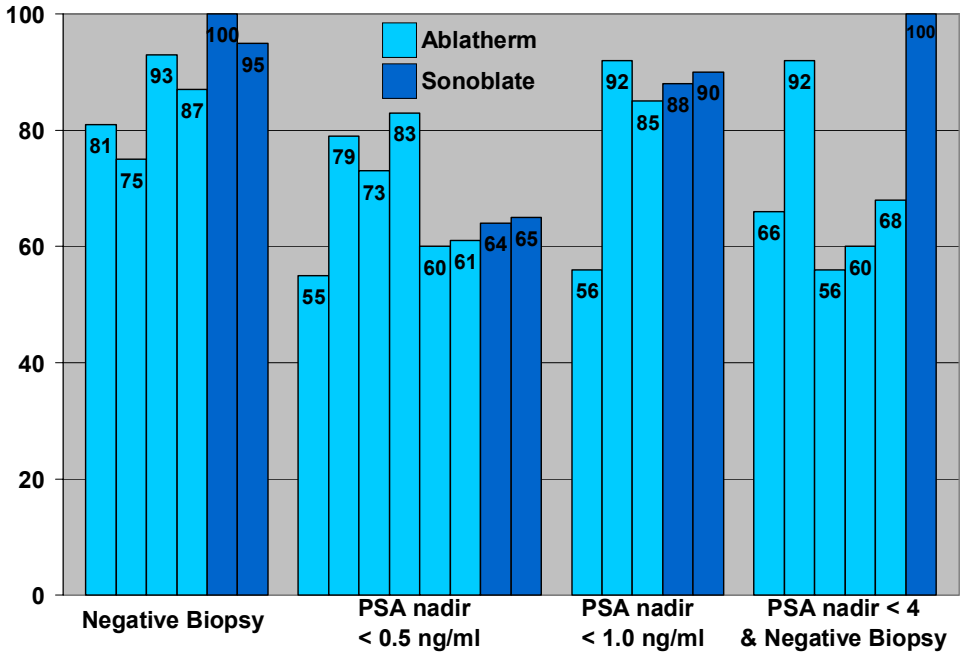

Figure 2. Comparison of negative biopsy, <0.5 and <1.0 ng/ml PSA nadir and combined negative biopsy with nadir <4ng/ml results obtained with the Ablatherm and Sonablate devices.

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