

HIFU TREATMENT DATA IS MATURING



By Nathan Roundy

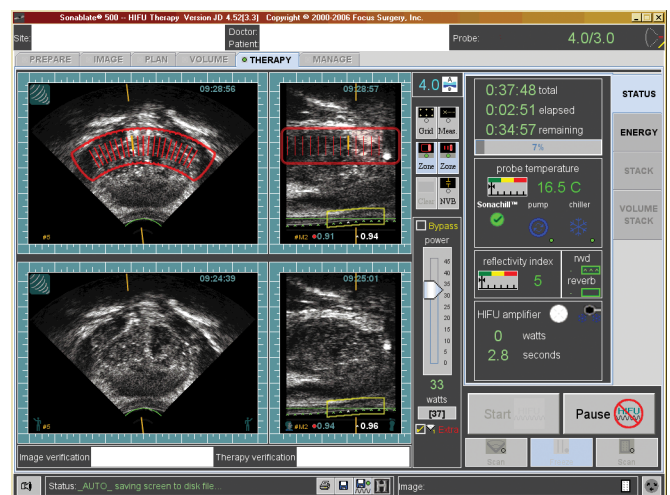
High Intensity Focused Ultrasound (HIFU) is an appealing treatment for prostate cancer. It is advertised to be minimally invasive, performed in a single day, and possibly has somewhat fewer side-effects (such as impotence, incontinence, and bowel damage) compared to some other therapies. Many men receiving HIFU remain cancer free for years.

HIFU is performed with an ultrasound probe inserted into the rectum. The ultrasound generates high energy sound pulses which are focused to repeatedly heat small areas of the prostate until the gland and the cancer cells are eradicated by the heat.

There are two HIFU device manufacturers, Ablatherm and Sonablate. Readers are referred to the paper on the PCRI web site by Dr. Doug Chinn, referenced at the end of this article, for a discussion of the advantages of each.

When a man has PSA rising after external radiation, HIFU can be used as 'salvage' therapy in hopes of eradicating the remaining cancer in the prostate. This paper does not discuss the salvage option.

Prostate cancer treatment failure is usually first identified by a rising PSA and that often requires years to become apparent. Early reports of HIFU treatment outcomes had short follow-up. So instead of using long-term PSA failure rates, these reports used non-standard measures of treatment success such as repeated prostate



biopsies. The results of these early reports were encouraging and got a lot of positive press. Many doctors started using HIFU to treat prostate cancer. It was hoped HIFU would result in cure rates that were higher, or at least as good, as prostatectomy or radiation.

Long-Term HIFU Outcomes Disappointing

The ‘Kaplan-Meier’ graphs below show the PSA relapse-free Disease Free Survival rates (DFS) from two of the more important published HIFU studies(1,2). The curves show how many men had prostate cancer recurrence over time. To understand Figure 6, at top left of the graph, the green, blue and

does not mean overall survival or death. Biochemical Relapse-Free Survival refers to PSA not rising.

Men considering treatment options want to know if HIFU offers better PSA Relapse-Free Survival than prostatectomy or radiation therapy. To do that, one can try to compare scientific reports of how many men failed therapy and had PSA rising (biochemical

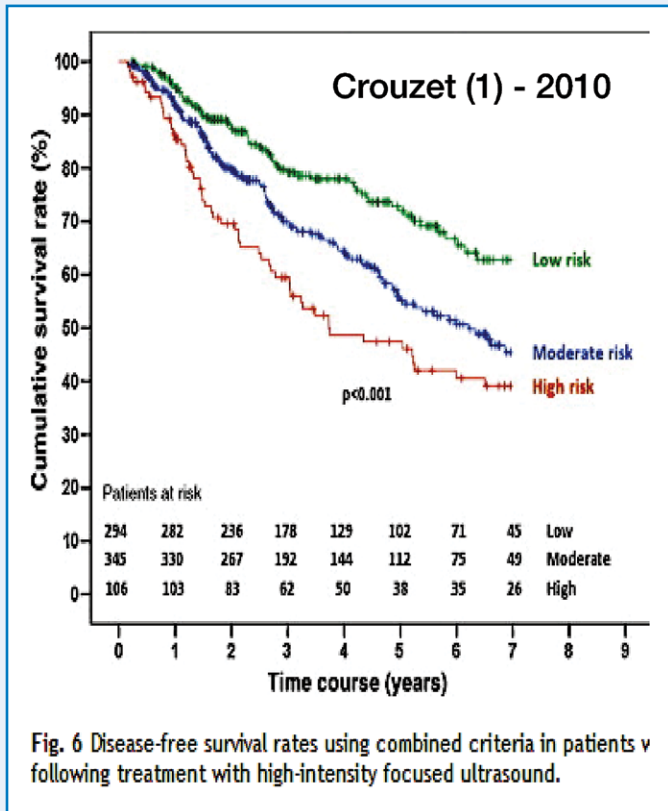
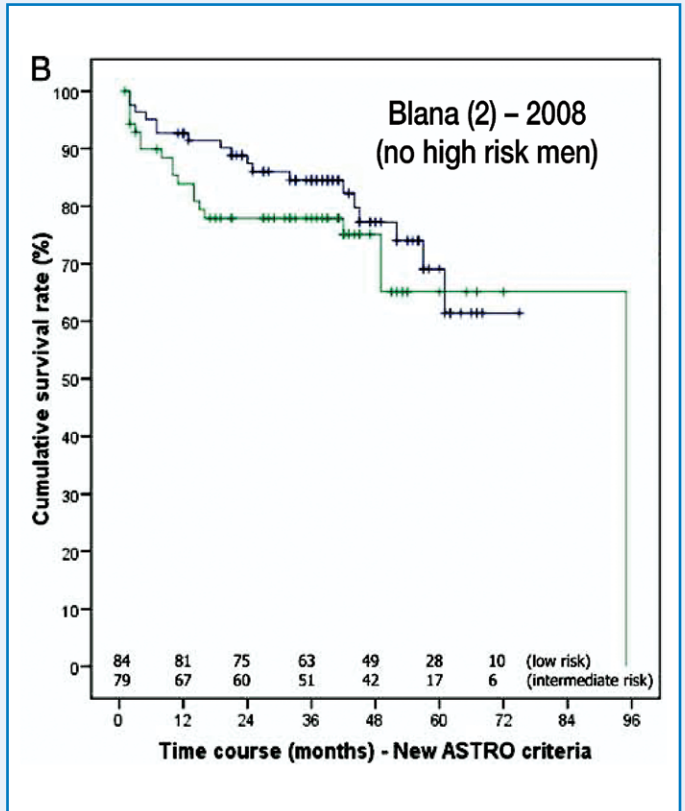


Fig. 6 Disease-free survival rates using combined criteria in patients v following treatment with high-intensity focused ultrasound.



red lines show that initially 100% of men immediately after treatment are deemed to be recurrence free. Over time, as the line moves across the graph (and down) to the right, more and more men have recurrence. After seven years, about 38% of men with the *Low-Risk* disease had the cancer come back. Only 39% of the men with *High-Risk* disease were still cancer free after seven years. Note that the curves are still trending down and more men will experience failure with time.

failure). Unfortunately it is very difficult to accurately compare HIFU reports of Biochemical Relapse-Free Survival to Prostatectomy or Radiation therapy reports because of the HIFU reports use non standard and varying definitions. As you read the following you will see how the definition of HIFU failure varies.

Different Definitions of Biochemical (PSA) Relapse-Free Survival

PSA rising after therapy is an early indication treatment has failed. In scientific papers freedom from PSA rising is measured and reported as Biochemical Relapse-Free Survival. In this context ‘survival’

PROSTATECTOMY

1. failure includes all men who had PSA rising to 0.2 ng/ml
2. failure includes all men who initiated any salvage therapy

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Table 1. HIFU SURVIVAL DEFINITIONS ⁽¹⁾			
	Low Risk	Intermediate	High Risk
Biochemical Disease-Free Survival (7 year) (Def #1)	75%	63%	62%
Disease Free Survival (7 year) (Def #2)	62%	46%	39%

Use HIFU Disease Free Survival, not HIFU Biochemical Disease Free Survival to compare HIFU studies to prostatectomy and radiation study Biochemical Relapse Free Survival.

RADIATION

1. failure includes all men who had PSA rise 2 ng/ml above the lowest nadir (Phoenix Definition)
2. failure includes all men who initiated salvage therapy

**HIFU Failure Rate Definition #1:
PSA Relapse-Free Survival**

1. failure includes men who reached the Phoenix Definition of failure
2. failure *does not* include men who had a positive biopsy after HIFU and got early salvage therapy
3. failure *does not* include men who had rising PSA after HIFU, but got early salvage therapy before reaching the Phoenix Definition of failure (rise of 2 ng/ml above the lowest nadir)

**HIFU Failure Rate Definition #2:
Disease-Free Survival (more similar to prostatectomy and radiation)**

1. failure includes men who reached the Phoenix Definition of failure
2. failure includes men who had a positive biopsy after HIFU and got early salvage therapy
3. failure includes men who had rising PSA after HIFU, but got early salvage therapy before reaching the Phoenix Definition

Removing men who had positive biopsy, or early salvage therapy (using Definition #1), makes it impossible to

compare HIFU biochemical survival with prostatectomy or radiation Biochemical Survival.

Crouzet(1) uses Definition #2 of “Disease Free Survival” which includes all men who failed HIFU, including those who got some type of early salvage therapy. To compare outcomes of HIFU with outcomes of surgery or radiation, Disease Free Survival (Def. #2) not Biochemical Survival (Def#1) needs to be used. Read the Crouzet paper for explanation. Table 1 shows how big a difference there is using the different definitions.

Side Effects

HIFU causes some men to become impotent, incontinent, or to have bowel problems, just as do all the other prostate cancer treatments. For example Uchida(3) reports 28.9% of previously potent men became impotent after HIFU. Blana(2) reports 44% impotent after HIFU. Some HIFU studies claim less severe side effects compared to prostatectomy or radiation, but side-by-side comparison papers have not been located.

Practice Makes Perfect

It has been clearly demonstrated that prostatectomy surgeons with increased yearly caseloads have lower complication rates. Moreover, it has been shown that a surgeon needs to conduct at least 250 radical prostatectomies to maximize cancer control(16). Radiation oncologist Lisa Chaiken from Los Angeles, says radiation treatment planning and execution for prostate cancer is complex and her estimate is it probably takes a similar number (250) of cases to become expert. We can speculate that similar training is required for a doctor to become expert in

HIFU treatment. The PCRI recommends, before choosing a doctor, to ask potential doctors how many cases they do per week, per year, and how many cases done in total. Ask if they keep track of and publish their patient's treatment side effects and relapse-free survival rates.

Salvage After HIFU Failure

If a positive biopsy or PSA rising indicate a man failed HIFU treatment, there are at least three salvage therapy options that may give a long PSA remission. Unfortunately, adding these salvage therapies may also increase the side-effects and quality of life issues.

- Salvage HIFU – HIFU can be repeated in hopes of killing remaining cancer in the prostate.
- Salvage Prostatectomy – Lawrentschuk(13) reported on 11 men who underwent prostatectomy after failing HIFU. After median 12 months, 10 of 11 men had undetectable PSA and number 11 was on hormone therapy. Most did not have to use pads for incontinence, but impotence was common.
- Salvage Radiation -- Ripert(15) reported on 83 men who failed HIFU and got salvage radiation with median dose 72 gy. Progression Free Survival was 93%, 67%, and 55% for the *Low-*, *Intermediate-*, and *High-Risk* groups, respectively.

Evaluate Treatment Option

Ideally, all studies would use the same definition of:

1. prostate cancer risk from the original clinical diagnosis (low, intermediate, high risk)
2. definition of treatment failure
3. PSA free outcomes by risk stratification
4. side effects

Unfortunately, no such standards exist. Non-standard reporting in scientific papers make comparison of various treatment outcomes difficult. Understanding that, a man facing these choices has to study the available evidence and make a decision to treat or not to treat. And, if treatment is decided, choose for himself which therapy provides the best tradeoff between convenience, side effects, and PSA free survival.

The data in Table 2 comes from an Internet search of www.PubMed.gov and other sites for HIFU, along with other treatment modality scientific papers with the following characteristics.

- Long follow up
- Large sample size
- Excellent PSA free survival

Table 2 is not a complete list, but is intended to illustrate some of the important details from the various studies. The reader is cautioned to read the individual reports to try to understand how they may apply to a man comparing treatments, and to consult with the patient's medical team before making any treatment decisions.

Keep in mind that the studies in Table 2 are from the most experienced HIFU doctors who are leaders in their fields. Doctors who do more procedures and who collect and report their outcomes are more likely to have good results. Doctors with low treatment volume and less experience may not achieve the same levels of success. Also, newer prostate cancer treatment tools, software, and improved technology is changing the treatment outcomes and making older studies obsolete for comparison.

In summary, this article compares reported treatment outcomes from the largest and longest HIFU papers with similar articles from experts in other therapies. Although not a comprehensive review of all the competing options, we hope it helps men with prostate cancer to better understand how to evaluate their treatment options.

Note: This Insights article refers the reader to many scientific papers available on the Internet. It is much easier 'click' from inside your Internet browser by first downloading the electronic copy of this Insights on our web site . Go to www.pcri.org and click on Insights. Or <http://www.prostate-cancer.org/pcricms/node/59>.

Learn About HIFU – You can read a detailed 2005 report on our web site here [Transrectal High Intensity Focused Ultrasound: The Next Generation?](http://www.prostate-cancer.org/pcricms/node/186) • HIFU • Douglas O. Chinn, MD 2005 <http://www.prostate-cancer.org/pcricms/node/186>

HIFU treatment for prostate cancer is not yet approved in the USA because the required clinical trials are not completed.

You can learn about clinical trials here <http://www.prostate-cancer.org/pcricms/node/37>

See available HIFU clinical trials here <http://www.clinicaltrials.gov/ct2/results?term=prostate+hifu>

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TABLE 2. Recent HIFU, Cryotherapy, Brachytherapy, and Prostatectomy scientific papers. ©The Prostate Cancer Research institute. 01/09/2011

AUTHOR	YEAR	NUM. MEN	FOLLOW-UP (Mo.)	DFS* LOW RISK	DFS * INTERMED.	DFS * HIGH RISK	DFS * ALL	INCONTINENCE
HIFU Papers								
Uchida ^(3,4)	2009	517	24	84% 5yr PSA<10	64% 5yr	45% 5yr	72% 5 yr.	
Crouzet ⁽¹⁾	2010	803	42	72% 5 yr 62% 7 yr	56% 5 yr 46% 7 yr	47% 5 yr 39% 7 yr		
Blana ⁽²⁾	2008	163	58	70% 5 yr	61% 5yr	no high risk	66% 5 yr	7.9%
Cryotherapy Papers (recur= 2 ng/ml rise)				BRFS** Low Risk	BRFS** Int. Risk	BRFS** High Risk	BRFS** All	
Jones ⁽⁷⁾ ***	2008	1198	60	91.1%	78.5%	62.2%	72.9%	4.8%
Brachytherapy ***				Low Risk	Int. Risk	High Risk	All	
Deutch ⁽⁸⁾ HDR + IMRT	2010	160	47	100% 5 yr.	98% 5 yr.	93% 5 yr.		
Taira, Merrick ⁽⁹⁾ Permanent Seeds	2010	1656	84	98.6%	96.5%	90.5%	95.6% 12yr	
Prostatectomy Papers				Low Risk	Int. Risk	High Risk	All	
Han and Walsh ⁽¹⁰⁾	2003	2091	70	97% 5yr	88% 5yr	51% 5yr	84% 5yr	7%
Catalona ^(11,12)	2004	3478	65				68% 10 yr.	7%
* DFS is HIFU Disease Free Survival ** BRFS is Biochemical Relapse-Free Survival (PSA) *** Phoenix Definition= 2 ng/ml above nadir **** RP= >=0.2 ng/ml								

For more information on comparing treatments, see the **Newly Diagnosed** section of our website. <http://www.prostate-cancer.org/pcricms/node/126>

The following papers are available for free as abstracts or complete papers. Use the Internet URL below the title to download the papers.

- Multicentric Oncologic Outcomes of High-Intensity Focused Ultrasound for Localized Prostate Cancer in 803 Patients. Sebastian Crouzet a,b,*, Xavier Rebillard c, Daniel Chevallier d, Pascal Rischmann e, Gilles Pasticier f, Gregory Garcia

g, Olivier Rouviere b,h, Jean-Yves Chapelon b, Albert Gelet a,b. 0302-2838/\$ – # 2010 European Association of Urology. Published by Elsevier B.V. All rights reserved. doi:10.1016/j.eururo.2010.06.037 [http://www.europeanurology.com/article/S0302-2838\(10\)00596-8/pdf/Multicentric+Oncologic+Outcomes+of+High-Intensity+Focused+Ultrasound+for+Localized+Prostate+Cancer+in+803+Patients](http://www.europeanurology.com/article/S0302-2838(10)00596-8/pdf/Multicentric+Oncologic+Outcomes+of+High-Intensity+Focused+Ultrasound+for+Localized+Prostate+Cancer+in+803+Patients)

- Eight Years' Experience With High-Intensity Focused Ultrasonography for Treatment of Localized Prostate Cancer. Andreas Blana, Sebastian Rogenhofer, Roman Ganzer, Jens-Claudio Lunz, Martin Schostak, Wolf F. Wieland, and Bernhard Walter. 0090-4295/08/\$34.00

1329 doi:10.1016/j.urology.2008.06.062 <http://www.institutodeprostata.com/descargas/8yearsexperienceHIFU.pdf>

- Ten-year Biochemical Disease-free Survival After High-intensity Focused Ultrasound (HIFU) for Localized Prostate Cancer: Comparison with Four Different Generation Devices. Uchida, T.; Nakano, M.; Shoji, S.; Omata, T.; Harano, Y.; Nagata, Y.; Usui, Y.; Terachi, T. 9th International Symposium on Therapeutic Ultrasound: ISTU-2009. AIP Conference Proceedings, Volume 1215, pp. 216-219 (2010) <http://download.journals.elsevierhealth.com/pdfs/journals/0022-5347/PIIS0022534710007949.pdf>

4. Quality of life following high-intensity focused ultrasound for the treatment of localized prostate cancer: a prospective study.
[Shoji S](#), [Nakano M](#), [Nagata Y](#), [Usui Y](#), [Terachi T](#), [Uchida T](#).
[Int J Urol](#). 2010 Aug; 17(8):715-9. Epub 2010 May 31. Department of Urology, Tokai University Hachioji Hospital, Hachioji, Tokyo, Japan. sunashoj@mail.goo.ne.jp
<http://www.ncbi.nlm.nih.gov/pubmed/20529139>
5. Transrectal high-intensity focused ultrasound (HIFU) treatment of localized prostate cancer: Review of technical incidents and morbidity after 5 years of use.
 Thomas Ripert, Marie-Dominique Azémar, Johann Ménard, Younes Bayoud, Rabah Messaoudi, François Duval and Frédéric Staerman [J Urol](#). 2008; Department of Urology and Andrology, CHU Reims, Reims, France
http://repository.peerproject.eu:8080/jspui/bitstream/123456789/2798/1/PEER_stage2_10.1038%252Fpcan.2009.57.pdf
6. Six years' experience with high-intensity focused ultrasonography for prostate cancer: oncological outcomes using the new 'Stuttgart' definition for biochemical failure.
[Ripert T](#), [Azémar MD](#); [Ménard, J](#); [Barbe, C](#); [Messaoudi, R](#); [Bayoud, Y](#); [Pierrevelcin, J](#); [Duval, F](#); [Staerman, F](#).
[BJU Int](#). 2010 Nov 17. doi: 10.1111/j.1464-410X.2010.09710.x. [Epub ahead of print]. Department of Urology and Andrology, and Clinical Research Unit, CHU Reims, Reims, France.
 PubMed Abstract PMID: 21083637
<http://www.ncbi.nlm.nih.gov/pubmed/21083637>
7. Whole gland primary prostate cryoablation: initial results from the cryo on-line data registry.
 Jones JS, Rewcastle JC, Donnelly BJ, Lugnani FM, Pisters LL, Katz AE. Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, Ohio, USA. <http://www.jurology.com/article/S0022-5347%2808%2900956-7/abstract>

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HIFU – NOT READY FOR PRIME TIME

By: Stanley Brosman, MD

HIFU is aggressively advertised as being less invasive and having fewer side-effects than surgery or radiation therapy, while achieving excellent cancer control. The reported clinical evidence does not prove those claims.

LESS INVASIVE ? – HIFU is conveniently performed in one day and is less invasive than surgical radical prostatectomy. It is more convenient than External Beam Radiation such as IMRT that requires daily radiation therapy for weeks. Brachytherapy with permanent seeds is also performed in a single day, but does require implantation of the seeds in the prostate. So, we agree HIFU is convenient and less invasive.

LESS SIDE EFFECTS? – We do not have good data to compare. In my urological practice in Los Angeles, we have treated quite a few men with HIFU side effects issues. Researchers in Ontario, Canada⁽¹⁾ reviewed the HIFU clinical evidence and published a HIFU Practice Guideline in August, 2010. This is their analysis of HIFU side-effects.

- ⤴ The common complications (medians) associated with HIFU included impotence (44% among previously potent patients), urinary tract infections (7.5% of patients), urethral stricture (12.3%), stenosis (7.8%), urinary incontinence (8.1%), urinary retention (5.3%), chronic perineal pain (3.4%) and urethrorectal fistula (1.0%).

EXCELLENT CANCER CONTROL? In Table 2 of this HIFU article, comparison of long term PSA control in published studies by centers of excellence, seems to indicate HIFU is near the bottom in long term PSA control.

BOTTOM LINE? HIFU remains an 'investigational therapy' until well designed clinical trials are completed and reported. Men in the USA interested in pursuing HIFU are encouraged to join one of the clinical trials underway.

- ⤴ Quoting the Canada study(1) – "Conclusion: HIFU is currently not recommended as an alternative to accepted curative treatment approaches for localized prostate cancer."
- ⤴ The French Association of Urology recommends HIFU as primary therapy only in lower-risk, older patients (>70 yr) with T1-T2 localized disease, Gleason score <7, PSA, 15 and a prostate volume < 40 cc.
- ⤴ The German urological association is not recommending the routine use of HIFU.

REFERENCES

1. **High-intensity focused ultrasound for prostate cancer: a practice guideline**
 Can Urol Assoc J. 2010 August; 4(4): 232–236.
 Himu Lukka et. al. Ontario's Program in Evidence-Based Care
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2910764/>

8. Comparison of PSA relapse-free survival in patients treated with ultra-high-dose IMRT versus combination HDR brachytherapy and IMRT. [http://www.jurology.com/article/S0022-5347\(05\)63946-8/abstract](http://www.jurology.com/article/S0022-5347(05)63946-8/abstract)
 Deutsch, I; Zelefsky, MJ; Zhang, Z; Mo, Q; Zaider, M; Cohen, G; Cahlon, O; Yamada, Y.
Brachytherapy. 2010 Aug 2. [Epub ahead of print]
 Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center New York, New York, NY.
<http://www.ncbi.nlm.nih.gov/pubmed/20685176>
9. Long-term Outcome for Clinically Localized Prostate Cancer Treated With Permanent Interstitial Brachytherapy. Taira, AV; Merrick, GS; Butler, WM; Galbreath, RW; Lief, J; Adamovich, E; Wallner, KE.
 Department of Radiation Oncology, University of Washington, Seattle, Washington.
Int J Radiat Oncol Biol Phys. 2010 Jun 2. [Epub ahead of print]
<http://www.ncbi.nlm.nih.gov/pubmed/20605342>
10. Biochemical (prostate specific antigen) Recurrence Probability Following Radical Prostatectomy For Clinically Localized Prostate Cancer. Misop Han, Alan W. Partin,* Marianna Zahurak, Steven Piantadosi, Jonathan I. Epstein and Patrick C. Walsh
The Journal of Urology®, February 2003, 0022-5347/03/1692-0517/0 vol. 169, 517–523
11. Potency, continence and complications in 3,477 consecutive radical retropubic prostatectomies. Kundu, SD; Roehl, KA; Eggener, SE; Antenor, JA; Han, M; Catalona, WJ.
J Urol. 2004 Dec;172(6 Pt 1):2227-31. Department of Urology, Feinberg School of Medicine, Chicago, Illinois 60611, USA.
<http://www.ncbi.nlm.nih.gov/pubmed/15538237>
12. [Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: long-term results.](http://www.drcatalona.com/journal/Rec_Surv_paper.pdf) Roehl, KA; Han, M; Ramos, CG; Antenor, JA; Catalona, WJ.
J Urol. 2004 Sep; 172(3):910-4. PMID: 15310996 [PubMed - indexed for MEDLINE] Free PMC Article
http://www.drcatalona.com/journal/Rec_Surv_paper.pdf
13. Biochemical Recurrence Following Robot-Assisted Radical Prostatectomy: Analysis of 1384 Patients with a Median 5-year Follow-up. Mani Menon a,d, Mahendra Bhandari a, Nilesh Gupta b, Zhaoli Lane b, James O. Peabody a, Craig G. Rogers a, Jesse Sammona,* , Sameer A. Siddiqui a, Mireya Diaz a,c
 a. Vattikuti Urology Institute, Henry Ford Hospital, Detroit, MI, USA
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 c. Department of Biostatistics and Research Epidemiology, Henry Ford Hospital, Detroit, MI, USA
- d. Case Western Reserve University, Cleveland, OH; New York University, New York, NY; European Association of Urology. doi:10.1016/j.eururo.2010.09.010 EUROPEAN UROLOGY 58 (2 0 1 0) 8 3 8 – 8 4 6
 University of Toledo Schools of Medicine, Toledo, OH, USA
<http://tinyurl.com/rarp-outcomes>
14. Salvage Radical Prostatectomy In Men Following High-Intensity Focused Ultrasound For Prostate Cancer. Nathan Lawrentschuk*, Antonio Finelli, Neil E Fleshner, Toronto, Canada; Damien Bolton, Melbourne, Australia; Theodore van der Kwast, John Trachtenberg, Laurence Klotz, Toronto, Canada; Henry Woo, Sydney, Australia
The Journal of Urology, Vol. 183, No. 4, Supplement, Sunday, May 30, 2010
<http://download.journals.elsevierhealth.com/pdfs/journals/0022-5347/PIIS0022534710007949.pdf>
15. Salvage radiotherapy after high-intensity focussed ultrasound for recurrent localised prostate cancer. Riviere, J; Bernhard, JC; Robert, G; Wallerand, H; Deti, E; Maurice-Tison, S; Ardiet, JM; Maire, JP; Richaud, P; Ferriere, JM; Ballanger, P; Gelet, A; Pasticier, G.
 Urology Department, Hôpital Universitaire Pellegrin, Bordeaux, France.
Eur Urol. 2010 Oct;58(4):567-73. Epub 2010 Jun 11.
<http://www.ncbi.nlm.nih.gov/pubmed/20598436>



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