

Recurrence of prostate cancer after HIFU. Proposal of a novel predictive index

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Summary. *Background and aim of the work:* Prostate cancer is one of the most common cancers in men over 50 years of age. Surgery, radiotherapy and hormonal manipulation represent its typical treatment. High-Intensity Focused Ultrasound (HIFU) is an alternative choice in localized prostate cancer. To date, an index for prediction of recurrence in patients treated with HIFU is not available. Our study proposes a novel index for the prediction of recurrence able to determine if a candidate is fit for this treatment. *methods:* 107 patients underwent HIFU from 2010 to 2015. A total of 12 variables were considered for the analysis. The final predictive model was obtained through a stepwise forward selection method. *Results:* The final model used a total of 6 variables, all correlated to the response variable. The Index is able to predict the recurrence after HIFU treatment in the most majority of candidates to treatment. The index may be used to make a more scientific decision with regard to choosing optimal candidates for HIFU. (www.actabiomedica.it)

Key words: HIFU, prostate cancer, recurrence, index, minimally-invasive techniques

Background and aim of the work

Prostate cancer is considered one of the most important topics in male health with an important social impact on the quality of life (1). In Europe, it is the most common solid neoplasm with an incidence rate of 214 cases per 1,000 men. It has become the second leading cause of cancer death in the majority of western countries (2, 3) and there is also a trend towards an increasing number of prostate cancer related deaths in Japan. The increasing life expectancy and the more and more widespread use of Prostate Specific Antigen (PSA) are probably the two most important reasons why more patients are diagnosed with prostate cancer (4).

Radical surgery represents one treatment option in men with clinically localized prostate cancer with a life expectancy of >10 years (5-7). Nevertheless, radical surgery itself can result in significant treatment-

related toxicity (8, 9). With equal survival outcomes, brachytherapy and Intensity Modulated Radiation Therapy (IMRT) offer good standard alternatives to surgery. Other minimally-invasive procedures such as cryotherapy and High-Intensity Focused Ultrasound (HIFU) are emerging as potential alternatives to the more standard options in elderly men whose medical comorbidities may make them less ideal candidates for either surgery or radiation therapy.

HIFU is an alternative choice in localized prostate cancer. It is a non-invasive technique inducing complete coagulative necrosis of a target tumour, without requiring surgical exposure or insertion of instruments into the lesion (10, 11). Since April 2006 we have been treating prostate cancer with HIFU (12); here we report our experience in 107 patients in addition to a simple probabilistic model to predict recurrence as a function of clinical preoperative determinants and patients' individual characteristics.

Methods

After obtaining local institutional approval, HIFU was introduced in our department routine. Initial training was received by an approved Ablatherm™ (EDAP, Lyon, France) committee. Also, our first treatments were performed under EDAP supervision. The selection criteria were as follows: cancer localized to the prostate or local relapse after radiotherapy with PSA <40 ng/mL, clinical stage (up to T3a), comorbidity (including anesthesia evaluation), age over 70. Exclusion criteria were: anal stenosis, previous rectal surgery, high prostatic volume (antero-posterior diameter more than 25 mm) and coxo-femoral ankylosis. All patients were given counselling about the investigational nature of the treatment and informed consent was obtained.

We included low-, intermediate- and high risk patients in accordance with the D'Amico classification (13): low risk, clinical stage T1c or T2a, Gleason score ≤6 and PSA ≤10 ng/mL; intermediate risk, PSA 10–20

ng/mL or Gleason score 7 or clinical stage T2b; high risk, PSA >20 ng/mL or Gleason score >7 or clinical stage ≥T2b.

All patients underwent pre-treatment trans-urethral resection of the prostate (TURP): 7 underwent TURP at the same time of the HIFU procedure; 7 underwent TURP two months before; others had previously undergone procedures to increase flow (9 underwent adenectomy). Previous TURP also reduced the duration of catheterization. The characteristics of all patients are listed in Table 1. Tumours were staged using TNM staging system. None had metastatic disease.

To perform the treatment we used a Ablatherm™ device (EDAP, Lyon, France). It consists of a 3.0 MHz piezoelectric therapeutic applicator and a 7,5 MHz ultrasound scanner for treatment planning. Ablatherm® is 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 to keep the rectal mucosal temperature below 14°C and a monitor to set and

Table 1. Prognostic factors of disease progression. The GLZ model is $PSA_{rising} = g(Y)$ where Y is a linear regression model of the input variables. The regression for Y gave the above coefficients

	Univar. risk effect	Univariate 95% CI	Univariate p-value	Multivar. risk effect	Multivariate 95% CI	Multivariate p-value
Age	0,032	0,032±0,016	<0,001	0,027	0,027±0,031	<0,001
Gleason/TNM#	0,095	0,095±0,054	<0,001#	0,065	0,065±0,115	0,028
- Gleason score	0,121	0,121±0,074	0,002	0,065	#	#
- TNM	0,181	0,181±0,125	0,005	0,059	#	#
ln(PSA)	*0,114	*0,094±0,108	0,013	0,044	0,044±0,148	0,242
IIEF	0,003	0,003±0,009	0,538	0,007	0,007±0,016	0,082
TUR-P	-0,059	-0,059±0,149	0,429	-0,095	-0,095±0,244	0,125
Adenectomy/TUR-P#	0,084	0,084±0,116	0,151#	0,073	0,073±0,193	0,133
- Adenectomy	0,125	0,125±0,199	0,212	0,073	#	#
- TUR-P	-0,102	-0,102±0,164	0,216	-0,059	#	#
IPSS	*-0,004	*0,014±0,068	0,091	not included		&0,486
N-ADT	0,077	0,077±0,157	0,331	not included		&0,524

See text.

* Y shows a nonlinear dependence on these variables, in the univariate model. The p-value comes from a quadratic fit. In the table, the main coefficient is replaced by the rate of variation at median point. The confidence interval is replaced by the range of the rates of variation at extreme points.

& the selection of variables followed a stepwise forward approach. Variables entered the model in the order of this table. The procedure stopped before the insertion of the last two variables, which would result in the given p-values.

control the treatment procedure through echographic screening.

All patients were regularly assessed based on post-HIFU PSA levels at 3, 6, 12 months, and then every 6 months. Prostate sextant biopsies were performed 6 months after HIFU treatment, regardless of PSA. Prostate biopsies were also performed again during follow-up in cases of a rising PSA.

The functional outcome was assessed using IPSS and IIEF scores: Urinary symptoms and sexual potency were evaluated by IPSS - International Prostate Symptom Score (0-7 Mildly symptomatic; 8-19 Moderately symptomatic; 20-35 Severely symptomatic) and IIEF5 - International Index of Erectile Function 5 (6-10 High erectile deficit; 11-16 Moderate deficit; 17-25 Low deficit; 26-30 No deficit). We collected IPSS and IIEF data before treatment and 6 months later. Incontinence data were collected from patient-reported outcomes on leakage and pad usage. Treatment failure was defined by several criteria: first of all, biochemical failure assessed using Phoenix definition (PSA nadir + 2 ng/mL) (14); starting salvage therapy, such as radiotherapy (RT) or androgen depriving therapy (ADT); and the presence of cancer on biopsy after treatment.

Data collected during follow-up was analyzed looking for risk factors. The response variable was a PSA_rising, i.e. the highest increment observed in the PSA level between the nadir point and any subsequent value during the follow-up:

If t_0 is the time of the nadir point during follow-up,

$$\text{PSA}_{\text{rising}} = \max_{t > t_0} \text{PSA}_t - \text{PSA}_{t_0}.$$

By the Phoenix definition, biochemical failure occurs when PSA_rising is greater than 2 ng/mL.

Since PSA_rising inside the sample showed a distribution very far from Gaussian and highly right-skewed, it was impossible to fit the data with simple linear models, so we implemented a generalized linear model (GLZ) instead. This means that we had to introduce an intermediate “dummy” risk variable Y .

The variable Y is linked to PSA_rising through the empirical nonlinear function g represented in Figure 1. Y ranges from 0 to 1, higher values corresponding to higher levels of PSA_rising. In particular PSA_rising is above 2 ng/mL whenever $Y > 0.72$. The distribution Y

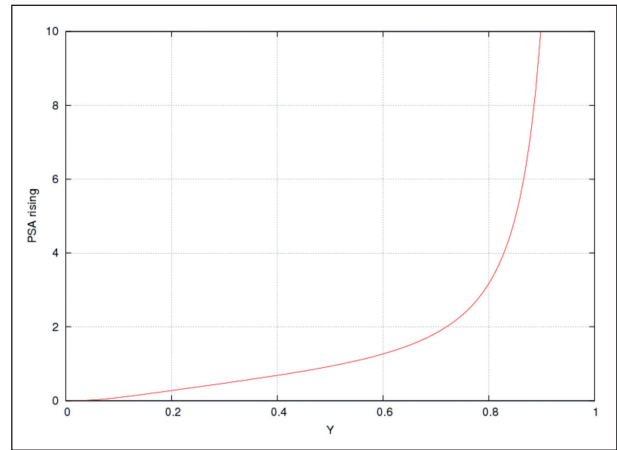


Figure 1. Graph of the nonlinear function g used in the GLZ model for PSA_rising

is not very far from Gaussian and roughly symmetrical, and it was possible to fit its values with a standard multilinear regression model.

A total of 12 input variables were initially considered for the analysis, almost all of which were found correlated to the response variable (see Table 2). The final predictive model for Y was obtained through a stepwise forward selection method.

Age, TNM and Gleason score before HIFU were significantly linked to the PSA rising after treatment, and the PSA level before HIFU was somewhat significant. In the final multivariate model, all variables with a possible contribution ($p < 0.3$) were included, meaning that also IIEF, TURP, ADENOMECTOMY and TUR-P (Trans-Urethral Resection of Prostate performed before HIFU treatment) were used, while IPSS and N-ADT (Neo-adjuvant Androgen Depriving Therapy) showed no contribution whatsoever and were left out. TNM and Gleason score were strongly positively correlated (regression $p < 0.001$). Variables ADENOMECTOMY and TUR-P were strongly negatively correlated (Fisher's exact test $p < 0.001$). For this reason Factor Analysis was used to extract one single factor from each of the two couples.

The final model used a total of 6 variables. Two of them are factors which might be expanded in 4 variables, for a total of 8 coefficients. Of course statistical inference can be done only for the 4 proper variables and 2 factors, and not for the 4 hidden variables (see # in Table 1).

Table 2. Table for prediction of recurrence after HIFU using the Parma Hifu Index (examples)

id	Age	PSA	Istology	TNM	IIEF	TURP	Adenectomy	TURP PRE HIFU	predicted PSA rising	prob >2
201	72	6.2	G3(3+3)	T1C	11	NO	NO	SI	0.8	10%
202	78	5.3	G4(4+3)	T1B	15	SI	SI	SI	1.7	44%
203	76	1.69	G3(3+3)	T1C	21	SI	NO	SI	0.9	14%
204	68	1.27	G4(4+3)	T2A	12	NO	NO	NO	0.8	15%
205	55	4.3	G3(3+3)	T1A	10	NO	NO	NO	0.0	too far from training set
206	85	5.5	G5(5+4)	T1B	9	SI	NO	SI	8.7	76%
207	70	6.83	G3(3+3)	T1A	18	SI	NO	SI	0.6	5%
208	80	30	G3(3+3)	T3B	20	NO	SI	NO	40.0	82%
209	72	3.4	G3(3+3)	T1C	15	SI	NO	SI	0.6	5%
210	68	17.5	G3(3+3)	T2A	21	NO	NO	SI	1.0	18%
median	72	6.2	G3(3+3)	T1C	11	NO	NO	SI	0.8	10%

Results

A total of 107 HIFU procedures were performed over a 4-year period (between April 2010 and December 2015). Thirty-two patients who underwent first line treatment were excluded because of follow-up <1 year as the procedure was performed in the last few months (n=19), because they had their follow-up elsewhere (n=4) or because they were not suitable for statistic evaluation (n=6). Three patients were lost to follow-up.

Of the remaining 75 patients, the age range was 56 to 82 with a mean of 72.28 (± 4.63) years.

The percentages of high-, intermediate- and low-risk categories of D'Amico (13) were 13.3% (n=10), 25.3% (n=19) and 61.4% (n=46) respectively, with a mean (SD) PSA level of 9.44 ng/mL (± 11.05) ng/mL. Specifically, mean PSA level was 24.01 (± 23.25) ng/mL, 10.34 (± 5.44) ng/mL and 5.8 (± 2.64) ng/mL in the high-, intermediate- and low-risk categories. Seventeen patients (22.7%) had received neoadjuvant therapy (NADT) for three months and this was discontinued immediately after HIFU. Only seven patients underwent TURP at the same time of HIFU-procedure. Mean catheterization time was 9.3 days (± 4.5). On the whole, 3 patients required interventions for either a stricture or endoscopic removal of necrotic tissue within the prostate cavity. The overall mean PSA nadir was 1.19 ng/mL, with a median of 0.6 and

a range of 0.065-25,3 ng/mL and was obtained within a mean range of 3 ± 2.3 months. A nadir value ≤ 0.2 was obtained in 34.6% (n=26). The nadir value was ≤ 1 in 68% (n=51).

Using the Phoenix criteria for biochemical failure, HIFU failed in 17.3% of the patients (n=13) during a mean follow-up of 29.9 months (median 15 months, range 9-40 months). Stratification of failure by D'Amico criteria (6) was: out of the 13 failures, 30.4% high-risk (n=7); 15.3% intermediate-risk (n=2); and 30.7% low-risk (n=4). In the high-risk group, failures were 70% (n=7), in the intermediate-risk group 10.5% (n=2) and in the low-risk group 8.6% (n=4). Mean time to failure was 12.5 months, with a range of 3-40 months. During the follow-up period, 45 patients had prostate biopsies: 15.5% (n=7) were positive. All these patients had biochemical failure.

At 3 months after HIFU, 13 (17.3%) patients complained of urinary incontinence. In 6 of these patients urinary incontinence was transient and resolved in 6 months. In the other 7 patients it was still present after twelve months (2 pads/day). They were investigated with urodynamic evaluation: 5 were successfully treated with anticholinergic drugs; 2 were diagnosed with sphincteric incompetence and required artificial sphincter (AMS-800™).

The mean change in IPSS score was -3.46 (± 5.62). Sexual potency was defined according with the IIEF

score system. 16 patients were potent before HIFU. Four men regained potency after HIFU. Four patients were partially impotent (a degree of erectile function was present but sexual intercourses were not possible) 6 months after HIFU. 5-phosphodiesterase treatment was recommended to these patients. IIEF score mean change was 10.5 (± 7.44). There was one recto-vesical fistula (in the salvage group) (15). Diagnosis was provided by flexible cystoscopy and cysto-urethrogram. This patient was managed with prolonged catheterization, as he declined any surgical procedure. The procedure was well tolerated and no intra-operative or peri-operative deaths occurred.

Statistical analysis of data was based on a multi-linear regression model for the “dummy” variable Y, which is linked to PSA_rising through the empirical nonlinear function g showed in Figure 1. Values of Y greater than 0.72 correspond to values of PSA_rising greater than 2 ng/mL, i.e. to biochemical failure according with Phoenix criteria.

The final estimated predictive model for Y is the following:

$$Y = -2.058 + 0.027 * AGE + 0.065 * GL + 0.059 * T + 0.044 * \ln PSA + 0.0069 * IIEF - 0.095 * TURP + 0.073 * ADENOMECTOMY - 0.059 * TURP_PRE$$

Here GL is a modification of the classical Gleason score: if Gleason is (a+b), then $GL = 1.2 * a + 0.8 * b$. T is the numeric value of T in TNM classification. TUR-PRE is a short for TUR-P pre-HIFU. The last three variables are encoded with Yes=1 and No=0.

The Microsoft Excel spreadsheet (available upon request to the corresponding Author) allows the user to get a prediction for the value of PSA_rising and for the probability of biochemical failure, given the input variables, as in the following examples (Table 2).

Discussion

Currently there are different approaches in the management of localized prostate cancer. Traditional standard interventions, such as radical prostatectomy (radical retropubic prostatectomy and robotic-assisted laparoscopic prostatectomy) and radiation therapy (IMRT and Brachytherapy) have undergone many

technical refinements in the last few years, in order to improve clinical outcomes.

Madersbacher and colleagues reported the first localized prostate cancer successfully treated with HIFU in 1995 (16) and Gelet et al published the first series in 1996 (17). Since then, HIFU has been considered as a possible alternative choice in the management of localized prostate cancer.

In 2010, Crouzet et al carried out a multi-center study on 803 patients, reporting an overall survival rate of 83% and a cancer-specific survival rate of 98% with a mean follow-up of 6.4 years, but more time and effort are needed to gain insight regarding treatment-related toxicities and oncologic outcome predictive factors (18).

In the present study, HIFU resulted in local control rates of 82.6%, which is consistent with the results reported for the other therapeutic treatment modalities. Reportedly, the risk of progression after radical prostatectomy is about 20% (19) and the “trifecta” outcome can be achieved in 62% (20). Older radiation therapy (EBRT) techniques result in higher rates of recurrence, however, newer techniques including IMRT and image-guided radiation therapy (IGRT) offer similar results to surgery and brachytherapy (21). Transperineal ultrasound-guided iodine-125 brachytherapy – with or without external beam irradiation – resulted in progression in about 20% of cases, although there are no randomized trials comparing brachytherapy with other curative treatment modalities (22–24).

To define the biochemical failure after HIFU, the Phoenix definition was used (2+PSA nadir value). There is no common agreement as to what constitutes biochemical failure after HIFU. Different definitions have been proposed and used by other investigators for biochemical failure, such as Stuttgart definition (25). However, in the largest reports to date of long-term follow-up after HIFU, the Phoenix definition is used (18, 26). In the present study, prostate biopsy was also performed, which added additional information by which to evaluate the efficacy of the HIFU treatment.

Our data show the clinical outcomes of 75 patients after HIFU, with a mean follow-up of 29.9 months. As it is clearly reported in Table 1, the highest rate of biochemical failure was found in the high-risk group (70%), while the lowest rate was found in

the low-risk group (8.6%). The high rate of failure found in the high-risk group may also be attributed to the small number of high-risk patients treated with HIFU. The most favorable outcome is reported in low- and intermediate-risk group. This correlates well with the results reported by many investigators.

Univariate and multivariate analysis was carried out in order to highlight some predictive factors of recurrence after HIFU. As it is shown in Table 2 the most important predictive factors are age, Gleason score and TNM. Pre-treatment PSA value has a less important predictive role but still maintains a probabilistic value. Also, other factors such as IIEF score, TUR-P pre-HIFU have been investigated, showing that they have a less important but not meaningless predicting value. To our knowledge, there are no data in the literature correlating the clinical outcome after HIFU treatment with the predictive factors we deal with. Our data show that some patient characteristics related to the performance status, such as the preoperative IIEF score, contributes to the overall outcome of the treatment, thus suggesting that healthy patients have a better chance to positively respond to the treatment. One hypothesis may be that healthy patients have a healthy immune system, and the immune response is known to be increased in the ablation area (27). This hypothesis, however, needs to be studied further.

In actuality, unlike other solid malignancies, the prognosis of HIFU-treated prostate cancer is not solely dependent on tumor burden but is also influenced by many other patient characteristics. As a consequence, a staging system such as TNM and the Gleason score are not able to predict recurrence after HIFU treatment, as they rely on purely pathological variables. There is a need, therefore, for a reliable prognostic score that can be utilized in routine clinical practice to determine the individual risk of recurrence for patients undergoing HIFU treatment.

Data collected during the course of this study were analyzed in order to produce a training set with the aim of developing an index predictive of recurrence after HIFU. The Index has been called Parma HIFU recurrence Index (PHrI).

A common concern of the treating oncologist has been to find a selection system useful in defining which patients might benefit from this minimally-invasive

treatment. The development of a novel index could afford the opportunity to make a more informed, scientific decision with regard to choosing optimal candidates for HIFU. Our model is a simple tool that could guide preoperative clinical decision-making regarding the indication to treat and may enable the physician and the patient to engage in a shared decision-making process before treatment and to determine the risks by evaluating preoperative data and individual patient characteristics.

Statistical evaluation demonstrates that all the variables included in the PHrI play a role in predicting recurrence after HIFU treatment. All these variables contribute to an Index that can be easily and cheaply obtained in routine practice prior to treatment. However, this study is based on a small number of patients, even if well selected. Therefore, it will be necessary to confirm these preliminary results in a multicenter trial in a larger patient cohort.

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