World Journal of Urology (2019) 37:2073–2080
https://doi.org/10.1007/s00345-018-2613-z

ORIGINAL ARTICLE

Oncological long-term outcome of whole gland HIFU and open radical prostatectomy: a comparative analysis

Bernd Rosenhammer[1] · Roman Ganzer[2] · Florian Zeman[3] · Theresa Näger[1] · Hans-Martin Fritsche[4] · Andreas Blana[5] · Maximilian Burger[1] · Johannes Bründl[1]

Received: 7 November 2018 / Accepted: 19 December 2018 / Published online: 2 January 2019

Abstract

Purpose To compare the oncological long-term efficacy of whole gland high-intensity focused ultrasound (HIFU) therapy and radical prostatectomy (RP) in patients with clinically localized prostate cancer.

Methods 418 patients after open RP (1997–2004) were compared with 469 patients after whole gland HIFU (1997–2009) without preselection. Oncological follow-up focused on biochemical relapse, salvage treatment, life status and cause-specific mortality. The univariate log rank test was used to compare both treatment options regarding overall survival (OS), cancer-specific survival (CSS), biochemical failure-free survival (BFS) and salvage treatment-free survival (STS). To adjust the treatment effect for further prognostic baseline variables, a multivariable Cox proportional hazards regression model was calculated for each end point.

Results Median follow-up was 13.3 years in the RP group and 6.5 years in the HIFU group. OS/CSS/BFS/STS rates at 10 years were 91/98/80/80% after RP and 76/94/70/71% after HIFU. HIFU therapy (reference RP) was a significant and independent predictor for an inferior OS, CSS and STS. In subgroup analysis, HIFU provided significantly reduced CSS for intermediate- ($p=0.010$) and high-risk patients ($p=0.048$); whereas no difference was observed in the low-risk group, intermediate-risk HIFU patients showed a significantly inferior STS ($p=0.040$).

Conclusions While whole gland HIFU offers a comparable long-term efficacy for low-risk patients, sufficient cancer control for high-risk patients is more than doubtful. For the subgroup of intermediate-risk patients, CSS rates seem to be comparable up to 10 years suggesting that HIFU may be an alternative for older patients, although a higher risk of salvage treatment should be expected.

Keywords HIFU · Radical prostatectomy · Oncological outcome · Prostate cancer

Introduction

High-intensity focused ultrasound (HIFU) has been studied since the early 1990s as an alternative primary treatment option for localized prostate cancer (PCa) with the intention to reduce morbidity of radical prostatectomy (RP) or radiotherapy. Moreover, HIFU can be used as a salvage treatment option for radiorecurrent PCa and may be repeated after failure of primary HIFU therapy [1, 2].

Despite a decent amount of data showing satisfying cancer control [3–10], there is ongoing controversy regarding whole gland HIFU as an equivalent modality compared to standard treatment options. The European Association of Urology (EAU) guideline, for example, does not recommend whole gland HIFU in the primary setting outside clinical trials due to the lack of long-term prospective and

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00345-018-2613-z) contains supplementary material, which is available to authorized users.

✉ Bernd Rosenhammer
bernd.rosenhammer@ukr.de

[1] Department of Urology, University of Regensburg, Caritas St. Josef Medical Center, Landshuter Str. 65, 93053 Regensburg, Germany

[2] Department of Urology, Asklepios Hospital Bad Tölz, Bad Tölz, Germany

[3] Center for Clinical Studies, University Hospital Regensburg, Regensburg, Germany

[4] Department of Urology, Surgical Clinic Munich-Bogenhausen, Munich, Germany

[5] Department of Urology, Fürth Hospital, Fürth, Germany

comparative data [11]. In fact, only few studies have been published providing oncological long-term outcomes after HIFU [12–14] and, moreover, no long-term data comparing HIFU with other curative treatment options are available. Although the concept of focal PCa therapy has gained more interest over the last years, oncological long-term results of whole gland treatment are essential to prove the safety and efficacy of the treatment modality.

Therefore, we conducted a retrospective comparative study evaluating the oncological long-term outcome after whole gland HIFU therapy vs. RP in patients with localized PCa.

Patients and methods

HIFU and prostatectomy databases were retrospectively analyzed and the oncological outcome of both procedures was compared. This single-center investigation was performed without any further patient preselection and all patients with clinically localized PCa and adequate oncological follow-up data (life status, cause-specific mortality, biochemical relapse and salvage treatment) were consecutively included before performing statistical analyses. Patients with a short-term pre-treatment androgen deprivation therapy (ADT) were not excluded. In such cases, pre-treatment ADT was not part of a neoadjuvant therapy concept, but was individually chosen by the referring urologists to offer the patient safety when the treatment decision was deferred for some weeks. In all cases, the clinical diagnosis was solely based on preoperative parameters.

In case follow-up was not carried out at our institution, data were provided by family doctors, referring urologists and registration offices according to patients' consent. The study protocol was approved by the local research ethics committee (Reference Number: 13-101-0272).

HIFU treatment and follow-up

All HIFU patients (1997–2009) were prospectively included and monitored after the procedure. HIFU was mainly offered to low-/intermediate-risk patients, but also to high-risk cases according to their wish. The majority of patients were treated by HIFU because they either preferred a less invasive treatment modality or were unsuitable for surgical treatment. Moreover, HIFU was offered as an option to patients with incidental PCa after TURP.

All procedures were performed using Ablatherm® devices (EDAP-TMS, Vaulx-en-Velin, France): 1997–2000 2nd Ablatherm® prototype device, 2000–2005 Ablatherm-Maxis®, 2005–2009 Ablatherm Integrated Imaging® device. In all cases, a safety margin of 4 mm from the apex was kept to spare the urethral sphincter. Pre-treatment transurethral resection of the prostate (TURP) was performed in the majority of patients to reduce prostate size and remove calcifications. In case of upstaging by TURP, e.g., by revealing a higher Gleason score, this was taken for the baseline characteristics.

Afterward, PSA measurements, digital rectal examination (DRE) and transrectal ultrasound (TRUS) were carried out at 3-month intervals. A systematic control biopsy was recommended to all patients at 3–6 months after treatment or in cases of rising PSA level. Patients who attended follow-up visits other than at our institution were contacted periodically. Biochemical progression was defined using the Phoenix criteria (PSA nadir + 2 ng/ml) [15].

Radical prostatectomy and follow-up

A total of 584 patients underwent open retropubic RP between 1997 and 2004. Afterward, open RP was replaced by laparoscopic RP at our institution (2005–2009). We therefore decided to exclude those patients, as inclusion might have influenced oncological results due to the associated learning curve of the new surgical approach in the beginning. Baseline characteristics were prospectively added to our database. In contrast to our HIFU group, follow-up data were collected retrospectively. After data collection, 146 patients (25%) had to be excluded as life status or cause-specific mortality could not be determined. Moreover, 20 patients were excluded because of advanced cT3 stage. Biochemical relapse was defined as two consecutive PSA values > 0.2 ng/ml.

Statistical analyses

Statistical analyses were performed using SPSS, version 24.0 (Chicago, IL, USA) and R, version 3.5.0 (The R Foundation for Statistical Computing). Comparing parametric variables, *t* test was used, while Mann–Whitney *U*-test was applied for non-parametric variables. Categorical variables were compared using chi-squared test.

The univariate log rank test was used to compare RP and HIFU, while Kaplan–Meier plots were used for graphical presentation. To adjust the treatment effect on overall survival (OS), cancer-specific survival (CSS), biochemical failure-free survival (BFS) and salvage treatment-free survival (STS) for further prognostic variables, a multivariable Cox proportional hazards regression model was calculated for each end point. p values < 0.05 were considered to indicate statistical significance.

Results

Patients

A total of 887 patients were included in the analysis, of whom 418 had received open RP and 469 whole gland HIFU therapy. Patient characteristics are shown in Table 1. Mean patient age in the HIFU group was 67.5 (SD 6.8) years and 62.8 (SD 5.6) years in the RP group ($p < 0.001$). As the majority of the HIFU patients underwent TURP before HIFU treatment, the mean prostate volume was lower compared to that of the RP group (21.4 vs. 30.2 cc, SD 7.8 vs. 12.3, $p < 0.001$). The distribution of low-, intermediate- and high-risk patients according to the d´Amico risk classification [16] did not differ between the two groups, although a slightly higher median PSA level was observed in the RP group (9.2 vs 7.1 ng/ml, $p < 0.001$). The majority of patients were classified as having low and intermediate risk. Only 4.1% of all patients had a preoperative Gleason score ≥ 8 and 11.0% had a preoperative PSA > 20 ng/ml. Preoperative short-term ADT was administered to 30.4% of the RP patients and to 37.1% of the HIFU patients ($p = 0.035$).

In the RP group, adjuvant/postoperative radiation was performed in 40 patients (9.6%) due to pT3b and/or R1 status revealed by the pathological evaluation of the surgical specimen. Moreover, 38 RP patients (9.1%) were diagnosed with lymph node disease. As a result, 30 of these patients (78.9%) were given ADT postoperatively.

Outcome

The maximum follow-up periods were up to 19 and 14 years after RP and HIFU, respectively. Median follow-up was 13.3 years in the RP group and 6.5 years in the HIFU group.

The Kaplan–Meier plots for OS, CSS, BFS and STS including the p values of the log rank test are depicted in Fig. 1. For BFS and STS analyses, 128 patients (14.4%) and 35 patients (3.9%), respectively, could not be included as the exact date of event could not be reliably determined.

In the multivariable Cox regression analysis (Table 2), HIFU proved to be an independent significant predictive factor for a reduced OS, CSS and STS compared to RP, while BFS marginally failed to gain statistical significance ($p = 0.072$). Moreover, patient age was predictive of a reduced OS while a positive DRE and a higher Gleason score were significant predictors for an inferior OS and STS, respectively. The preoperative risk category (d´Amico) was predictive of a reduced CSS and STS as shown in Table 2.

OS, CSS and STS rates for the whole population, stratified by treatment modality and risk classifications, are shown as supplemental data.

The OS rates at 5/10 years were 97/91% for the RP group and 91/76% for the HIFU group. Subgroup analysis according to preoperative risk stratification revealed an OS advantage of RP patients in all risk categories, but the differences were most significant in the intermediate- ($p < 0.001$) and high-risk groups ($p = 0.001$).

Table 1 Patient characteristics

Variable	Total ($n = 887$)	RP ($n = 418$)	HIFU ($n = 469$)	p Value
Age (years), mean (SD)	65.3 (6.7)	62.8 (5.6)	67.5 (6.8)	**< 0.001**
Prostate volume (cc), mean (SD)	25.4 (10.0)	30.2 (12.3)	21.4 (7.8)	**< 0.001**
PSA (ng/ml), median (IQR)	8.3 (5.4, 13.0)	9.2 (5.6, 15.4)	7.1 (5.3, 11.9)	**< 0.001**
Preoperative Gleason score, *n* (%)				
≤ 6	702 (80.2)	335 (80.1)	367 (80.3)	0.708
7	137 (15.7)	69 (16.5)	68 (14.9)	
≥ 8	36 (4.1)	14 (3.3)	22 (4.8)	
Preoperative DRE results, *n* (%)				
cT1	353 (41.8)	166 (44.1)	187 (39.9)	0.210
cT2/3	492 (58.2)	210 (55.9)	282 (60.1)	
D'Amico risk category, *n* (%)				
Low risk	405 (46.0)	196 (46.9)	209 (45.2)	0.118
Intermediate risk	344 (39.1)	151 (36.1)	193 (41.8)	
High risk	131 (14.9)	71 (17.0)	60 (13.0)	
Preoperative ADT				
No	586 (66.1)	291 (69.6)	295 (62.9)	**0.035**
Yes	301 (33.9)	127 (30.4)	174 (37.1)	

Bold values indicate p values <0.05 were considered statistically significant

RP radical prostatectomy, *DRE* digital rectal examination, *ADT* androgen deprivation therapy, *SD* standard deviation, *IQR* interquartile range

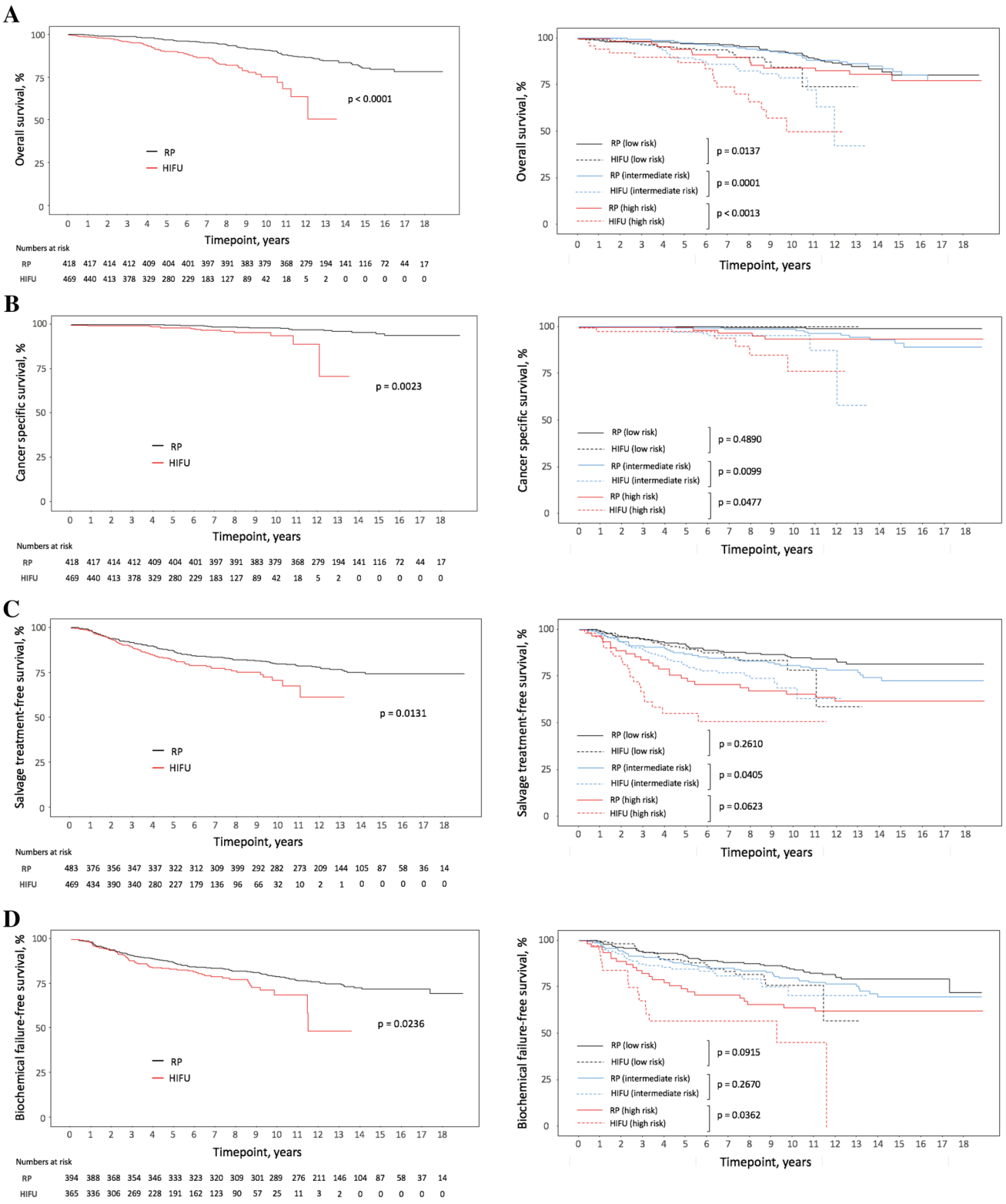

Fig. 1 Kaplan–Meier plots for **a** overall survival (OS), **b** cancer-specific survival (CSS), **c** salvage treatment-free survival (STS) and **d** biochemical failure-free survival after radical prostatectomy (RP) and HIFU. Plots for the whole collective are shown on the left and subgroup analyses on the right

Table 2 Multivariable Cox regression models for the end points: overall mortality, cancer-specific mortality, biochemical failure and salvage treatment

Prognostic factor	Overall mortality		Cancer-specific mortality		Biochemical failure		Salvage treatment	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
HIFU (reference: RP)	2.09 (1.33, 3.30)	**0.001**	4.00 (1.32, 12.08)	**0.014**	1.41 (0.97, 2.04)	0.072	**1.67 (1.16, 2.38)**	**0.005**
Age	1.05 (1.02, 1.09)	**0.001**	1.01 (0.94, 1.08)	0.870	1.02 (0.99, 1.05)	0.162	0.99 (0.96, 1.01)	0.218
PSA	0.99 (0.97, 1.01)	0.359	1.00 (0.97, 1.03)	0.823	1.01 (1.00, 1.01)	0.203	1.00 (1.00, 1.01)	0.412
Gleason score	1.05 (0.91, 1.22)	0.487	1.12 (0.82, 1.53)	0.487	1.13 (0.99, 1.29)	0.062	**1.19 (1.05, 1.35)**	**0.006**
DRE	1.79 (1.15, 2.79)	**0.010**	1.33 (0.47, 3.75)	0.587	1.27 (0.89, 1.80)	0.182	1.42 (0.99, 2.03)	0.055
D'Amico risk category								
Low risk	Reference	–	Reference	–	Reference	–	Reference	–
Intermediate risk	1.07 (0.67, 1.60)	0.774	7.45 (1.65, 33.74)	**0.009**	1.02 (0.70, 1.48)	0.932	1.23 (0.84, 1.79)	0.291
High risk	1.67 (0.80, 3.52)	0.176	5.82 (0.85, 40.07)	0.074	1.70 (0.99, 2.91)	0.056	**2.01 (1.18, 3.43)**	**0.011**
Preoperative ADT	1.56 (0.72, 1.55)	0.775	1.42 (0.62, 3.25)	0.411	0.96 (0.68, 1.35)	0.792	0.96 (0.69, 1.34)	0.812

Bold values indicate *p* values <0.05 were considered statistically significant

RP radical prostatectomy, *DRE* digital rectal examination, *ADT* androgen deprivation therapy, *HR* hazard ratio, *CI* confidence interval

CSS rates at 5/10 years were 99.8/98% for RP patients and 99/94% for HIFU patients. Whereas no difference was observed in the subgroup of low-risk patients, HIFU provided a significantly worse CSS in the intermediate- ($p=0.010$) and high-risk group ($p=0.048$). At 10 years, the CSS in high-risk patients receiving HIFU was 77% compared to 94% in the RP group, while CSS in intermediate-risk patients was comparable (99% after RP and 95% after HIFU).

The BFS rates at 5/10 years were 87/80% for the RP group and 84/70% for the HIFU group. The univariate log rank test proved statistical difference for the whole collective ($p=0.024$) and for high-risk patients ($p=0.036$).

The STS rates at 5/10 years were 87/80% for the RP group and 82/71% for the HIFU group. Whereas no difference was observed for low-risk patients, intermediate-risk HIFU patients showed a significantly worse STS compared to RP patients ($p=0.040$).

Discussion

The necessity of radical PCa treatment, particularly in patients with low-risk cancer, is more than ever under debate. Alternative treatment modalities have emerged with the attempt to achieve both sufficient cancer control and minimal morbidity. Among several techniques, HIFU has become popular, but its value is still not clear due to the lack of comparative oncological long-term data. Some interesting recent studies compared the outcome after HIFU and RP, but these studies provided short follow-up periods, included fewer or only preselected patients or performed partial ablation [17–20].

To our knowledge, the present study is the first to compare the oncological long-term efficacy after whole gland HIFU and RP without preselection excluding only locally advanced stages. Almost 900 patients of all risk categories were included and a maximum follow-up period up to 14 and 19 years, respectively, was provided. The quality of our collective was supported by the findings of the multivariable analysis.

Our data indicated an inferior oncological long-term outcome after HIFU compared to RP, as HIFU was an independent significant predictor for a reduced OS, CSS and STS in the multivariable analysis. Analyzing CSS rates in more detail, we found no difference between HIFU and RP in the low-risk group, but there was a difference in the intermediate- and high-risk group. Therefore, whole gland HIFU appears to be a reasonable alternative for low-risk PCa patients. In the subgroup of high-risk patients, CSS after 10 years declined to only 77% after HIFU, suggesting that these patients should not routinely be treated by HIFU in the primary setting. Concerning intermediate-risk patients, CSS rates were comparable between HIFU and RP after 5 and 10 years. Only beyond this period, the CSS after HIFU declined suggesting that HIFU might at least be an option for older patients. Summing up the CSS results, our study confirms previous findings of adequate long-term cancer control by HIFU for low- and intermediate-risk patients [12–14]. For the latter, however, CSS might deteriorate after 10 years.

As treatment modality was a significant and independent predictor for OS, we similarly analyzed OS rates based on preoperative risk groups and found inferior survival rates after HIFU throughout all risk categories. However, it has to be considered that the HIFU patients in the present study were around 5 years older than the RP patients and, therefore, comorbidities may have been more frequent. The lack

of a systematic comorbidity score evaluation is certainly a limitation of our study in this context. On the other hand, median patient age in the HIFU group was only 67.5 years and an average life expectancy of at least 10 years may reasonably be assumed for the majority of patients. In any case, the results of the multivariable Cox regression analysis strongly indicate that HIFU therapy is not only associated with an inferior long-term CSS, but also inferior OS compared to RP and the observed survival rates strengthen these findings. Potentially, the more frequently administered salvage ADT in the HIFU group might have caused relevant cardiovascular side effects and might be responsible for some non-cancer-specific events of death.

Biochemical recurrence and initiation of salvage treatment are further key events evaluating treatment success. According to the definition of BF after radiotherapy, the Phoenix criteria (PSA nadir + 2 ng/ml) are most widely used after HIFU treatment [15]. In contrast, BF after RP was defined as two consecutive PSA values > 0.2 ng/ml. Due to these differing definitions, we decided to include STS as an additional parameter to compare treatment success. Our data indicate both an inferior BFS and STS after HIFU compared to RP. Notably, the disadvantage in early cancer control within the first 5 years was most significant in intermediate- and high-risk patients. In this context, the evaluation of the surgical specimen has to be considered as a major advantage of RP in such patients. Apparently, this enables a correct local staging including lymph node evaluation and immediate adjuvant therapy can be initiated if indicated. For HIFU patients, this was not possible and some patients may have had higher tumor burden than estimated. Today, the availability of MRI has significantly improved this issue. In those days, however, MRI was not yet routinely established for local staging purposes which might have changed the treatment decision.

While contributing new comparative long-term efficacy data, our study provides oncological results which are in conformance with those reported in literature. With regard to the outcome after RP, our results are in line with large trials showing long-term CSS rates of 84.9–100% for low- and intermediate-risk patients [21–23]. Concerning long-term outcome after HIFU, Crouzet et al. reported an 8-year BFS (Phoenix definition) of 76/63/57% and a 10-year CSS of 99/98/92% for low-/intermediate-/high-risk patients [14]. Importantly, their baseline data and particularly the distribution of low-, intermediate- and high-risk patients were similar to our study. Compared to these data, only our high-risk patients showed a worse outcome. Possibly, this is due to the relatively low percentage of high-risk patients in both studies.

Another recent study compared the oncological outcome after whole gland HIFU and minimal-invasive RP for patients ≥ 70 years with ≤ cT2 disease, biopsy Gleason score ≤ 3 + 4 and preoperative PSA ≤ 10 ng/ml [18]. Applying the same definitions for BF, they reported a 5-year BFS of 78.9% after HIFU and 92.9% after RP while 5-year STS rates were 74.8% and 92.9%, respectively. Moreover, CSS rates were 100% for both procedures and 5-year OS was 97.1% after HIFU and 98.6% after RP. Apart from the somewhat worse 5-year BFS and STS rates after HIFU, these results are very similar to our results for the low- and intermediate-risk group.

In conclusion, our long-term data support previous mid-term results and provide further insights beyond the 10-year follow-up period. The strengths of our study are certainly the large number of almost 900 patients and the long follow-up period. Moreover, we included patients of all risk categories without preselection. All procedures were performed during a comparable era of PCa treatment which is particularly relevant, as the main end points of our study were CSS and OS. Though limited by the smaller number of high-risk patients, our data confirm that HIFU does not represent a safe option for these patients. Over the last years, the concept of focal therapy (FT) has emerged to reduce side effects of whole gland therapy, as tumor localization has been improved by the introduction of multiparametric MRI. In this context, our results strengthen current recommendations for clinical FT trials, as only low- and early intermediate-risk patients are considered appropriate candidates for inclusion [24].

Some limitations of our study have to be taken into account. Because of the retrospective approach, some patients could not be included in BFS and STS analyses and other important end points such as metastasis-free survival had to be excluded from the analyses as they could not be assessed in sufficient quality. Second, HIFU was performed using devices of different generations and a significant influence, at least on BFS, can be assumed as previously described by our group [12]. Moreover, we kept a safety margin of 4 mm to the sphincter during HIFU therapy. In patients with apical PCa localization, this could bias the results as recurrence rates could be higher in those patients. However, we assume that only few patients had a PCa located at the very apex within this margin and this may not extensively influence our findings. Third, the pathological workup has changed over the years. In 2005, the International Society of Urological Pathology (ISUP) modified the Gleason grading system [25], but all patients in our study were assigned to the d´Amico risk classification as currently defined. This has to be considered when interpreting subgroup analyses. In this context, we could not assess differences between ISUP grade 2 and 3 patients as defined nowadays, because in those days this was not routinely specified by the pathological specimen reports. A comparison of those groups, however, would be desirable for patient selection within the intermediate-risk group.

Finally, we do not provide functional outcome data as this was beyond the scope of this study. Insights into long-term quality of life, however, is a crucial issue when counseling patients with regard to less invasive treatment alternatives. Despite the oncological disadvantages of HIFU therapy, its potentially favorable side-effect profile might be another relevant point within the decision-making process.

Conclusion

Whole gland HIFU appears to offer a reasonable alternative to RP for patients with low-risk prostate cancer providing a comparable oncological long-term efficacy. In contrast, HIFU does not seem to guarantee sufficient cancer control for high-risk patients and should not routinely be performed in these cases. For the subgroup of intermediate-risk patients, CSS rates seem to be comparable up to 10 years suggesting that HIFU represents a reasonable option, at least for older patients, although a higher risk of salvage therapy has to be expected.

More studies with large collectives, subgroup analyses and long follow-up periods are certainly required to confirm our data and evaluate the long-term efficacy of HIFU therapy.

Author's contribution BR, JB: project development, data collection and analysis, manuscript writing; RG, AB, MB: manuscript editing; FZ: statistical analyses, manuscript editing; TN: data collection and analysis. HMF: project development, manuscript editing.

Compliance with ethical standards

Conflict of interest Johannes Bründl served as a paid instructor for EDAP-TMS. Andreas Blana served as a paid consultant for EDAP-TMS. The other authors declare that they have no conflict of interests.

Research involving human participants and/or animals This article does not contain any studies with animals performed by any of the authors.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol (reference number: 13-101-0272) was approved by the Ethics Committee of the University of Regensburg.

Informed consent For this type of study formal consent is not required.

References

1. Chaussy CG, Thuroff S (2017) High-intensity focused ultrasound for the treatment of prostate cancer: a review. J Endourol 31(S1):S30–S37
2. Jones TA et al (2018) High intensity focused ultrasound for radiorecurrent prostate cancer: a North American clinical trial. J Urol 199(1):133–139
3. Blana A et al (2008) Eight years' experience with high-intensity focused ultrasonography for treatment of localized prostate cancer. Urology 72(6):1329–1333
4. Crouzet S et al (2010) Multicentric oncologic outcomes of high-intensity focused ultrasound for localized prostate cancer in 803 patients. Eur Urol 58(4):559–566
5. Poissonnier L et al (2007) Control of prostate cancer by transrectal HIFU in 227 patients. Eur Urol 51(2):381–387
6. Uchida T et al (2006) Five years experience of transrectal high-intensity focused ultrasound using the Sonablate device in the treatment of localized prostate cancer. Int J Urol 13(3):228–233
7. Thuroff S et al (2003) High-intensity focused ultrasound and localized prostate cancer: efficacy results from the European multicentric study. J Endourol 17(8):673–677
8. Ficarra V et al (2006) Short-term outcome after high-intensity focused ultrasound in the treatment of patients with high-risk prostate cancer. BJU Int 98(6):1193–1198
9. Pfeiffer D, Berger J, Gross AJ (2012) Single application of high-intensity focused ultrasound as a first-line therapy for clinically localized prostate cancer: 5-years outcomes. BJU Int 110(11):1702–1707
10. Dickinson L et al (2016) Medium-term outcomes after whole-gland high-intensity focused ultrasound for the treatment of nonmetastatic prostate cancer from a multicentre registry cohort. Eur Urol 70(4):668–674
11. Mottet N et al (2017) EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 71(4):618–629
12. Ganzer R et al (2013) Fourteen-year oncological and functional outcomes of high-intensity focused ultrasound in localized prostate cancer. BJU Int 112(3):322–329
13. Thuroff S, Chaussy C (2013) Evolution and outcomes of 3 MHz high intensity focused ultrasound therapy for localized prostate cancer during 15 years. J Urol 190(2):702–710
14. Crouzet S et al (2014) Whole-gland ablation of localized prostate cancer with high-intensity focused ultrasound: oncologic outcomes and morbidity in 1002 patients. Eur Urol 65(5):907–914
15. Roach M 3rd et al (2006) Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 65(4):965–974
16. D'Amico AV et al (1998) Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 280(11):969–974
17. Albisinni S et al (2017) Comparing high-intensity focal ultrasound hemiablation to robotic radical prostatectomy in the management of unilateral prostate cancer: a matched-pair analysis. J Endourol 31(1):14–19
18. Capogrosso P et al (2018) Oncological and functional outcomes of elderly men treated with HIFU vs. minimally invasive radical prostatectomy: a propensity score analysis. Eur J Surg Oncol 44(1):185–191
19. Garcia-Barreras S et al (2018) Comparative analysis of partial gland ablation and radical prostatectomy to treat low and intermediate risk prostate cancer: oncologic and functional outcomes. J Urol 199(1):140–146
20. Chiang PH, Liu YY (2016) Comparisons of oncological and functional outcomes among radical retropubic prostatectomy, high dose rate brachytherapy, cryoablation and high-intensity focused ultrasound for localized prostate cancer. Springerplus 5(1):1905

21. Bill-Axelson A et al (2011) Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 364(18):1708–1717
22. Wilt TJ et al (2012) Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med 367(3):203–213
23. Hamdy FC et al (2016) 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med 375(15):1415–1424
24. van der Poel HG et al (2018) Focal therapy in primary localised prostate cancer: the European association of urology position in 2018. Eur Urol 74:84–91
25. Epstein JI et al (2005) The 2005 International Society Of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol 29(9):1228–1242