EDITORIAL

NEW NONINVASIVE TREATMENT OF PROSTATE CANCER WITH HIGH-INTENSITY FOCUSED ULTRASOUND (HIFU)

Following the diagnosis of Carcinoma prostate, patients are often confused by a wide range of treatment options offered to treat their disease. Both radical prostatectomy (RP) and external-beam radiotherapy (EBRT) have been shown to offer excellent long-term cancer control but are often associated with considerable side effects[1].

Standard treatment options such as RP and EBRT compete with various alternative options such as brachytherapy, cryotherapy, and high-intensity focused ultrasound (HIFU). What is the rationale to establish and favor carcinoma prostate treatment options other than RP and EBRT? It is mainly the physician's and the patient's quest to balance invasiveness, preservation of continence, and potency in combination with sufficient cancer control (i.e., the trifecta).

HIFU has been continuously developed and refined since the mid-1990s. The technology is based on ultrasound waves emitted from a transrectal transducer and focused on a target point with the immediate effect of coagulation necrosis in conjunction with limited damage to the surrounding tissue[2].

Obvious advantages demonstrated in the literature to date over EBRT are a short treatment period, short time to reach the PSA nadir, and several options for retreatment such as re-HIFU, salvage radiation, and salvage RP in case of local disease resistance or recurrence.

HIFU is approved in Canada, Europe, and Asia and has gained acceptance by the US Food and Drug Administration via an Investigational Device Exemption for a phase 3 clinical trial. European urologic associations make conflicting recommendations. HIFU is recommended in Italy, the United Kingdom, and France for selected patients. The French Association of Urology recommends HIFU as primary therapy for Carcinoma prostate in older patients (>70 yr) with T1–T2 N0M0 disease, Gleason score <7, PSA level <15 ng/ml, and a prostate volume of <40 ml[3]. In contrast, the German association is among those not yet recommending the routine use of HIFU in Carcinoma prostate.

What are the main reasons for patients to choose HIFU instead of standard treatment in primary CAP? It is the expectation of less invasiveness and unaltered quality of life. These expectations are driven by Web-based patient information with statements such as, "HIFU is an effective, non-invasive treatment that preserves the patient's quality of life"[4].

But do we currently have sufficient data to prove this? Overall and cancer-specific control is yet to be determined for HIFU, as the longest median follow-up for a multicentre series so far is 6.4 ± 1.1 yr[5]. In addition, there is no accepted standard definition of post-HIFU biochemical failure. A HIFU-specific failure definition (i.e., Stuttgart criteria) has been proposed but has not yet been validated[6].

What about side effects and quality of life? There are sufficient data on treatment safety with a treatment mortality of zero and low rectal toxicity with new-generation devices[4]. In comparison with RP, there seems to be a lower degree of stress urinary incontinence but a significantly higher rate of formation of bladder outlet obstruction[7]. Is there enough evidence to support superior outcome for potency? Rates for erectile dysfunction range from 20% to 49.8%. These data are controversial and limited by several facts; few of the studies used validated questionnaires before and after treatment. Most of men treated with HIFU were of advanced age, which is known to be associated with impaired baseline potency status. Some of the authors even present data following nerve-sparing HIFU; however, there is neither a clear definition nor a recommendation to treat in a non-full-gland-ablation approach outside of clinical trials. We feel that patients have to be informed about possible permanent damage to erectile function following full-gland HIFU treatment.

Against the background of the above-mentioned expectations in combination with controversial data, Warmuth et al are to be congratulated for their review of the efficacy and safety of HIFU for the primary and salvage treatment of CAP[8]. They conducted an extensive systematic literature search considering only prospective studies with >50 patients and assessed their quality using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

approach. Using the GRADE approach, they concluded that the available evidence on efficacy and safety of HIFU in CAP is of very low quality, mainly due to the lack of controlled studies.

Although quality and extensiveness of the review are remarkable, we would like to comment on some points. Why have studies with <50 patients not been included? Valuable information might have been missed. The "lack of control groups" is a problem for all accepted prostate treatments of localized CAP. Radical Prostatectomy is the only treatment option that was compared in a randomized controlled manner with watchful waiting[9].

It is important to note that 100 yr since the invention of RP, which is unquestionably the gold standard treatment for CAP, the highest-quality data allow one to conclude definitively that RP may be superior to watchful waiting. For prostate HIFU, which was invented about <20 yr ago, two US-based controlled trials are ongoing. One study compares HIFU with brachytherapy in organ-confined CAP with the primary end point being absence of biochemical failure at 24 months (NCT00770822). Another study compares biochemical outcome through a 24-month period between HIFU and cryotherapy (NCT00295802).

Warmuth et al's criticism regarding the lack of overall and cancer-specific survival data is justified, but one has to consider that HIFU is too new to draw any conclusions about its long-term cancer control. In addition, one has to be aware that sufficient oncologic follow-up data are not even available for intensity-modulated radiation therapy, brachytherapy, high-dose-rate techniques, or cryoablation and even laparoscopic and robot-assisted RP[9]. Therefore, we agree with Warmuth et al when they conclude that most of the limitations reported for HIFU also apply for all techniques of definitive CAP treatment.

One interesting future application of HIFU is focal therapy. HIFU offers the technology to discretely treat focal areas within the prostate with the aim of minimal side effects and leaves all options of secondary treatment such as re-HIFU, RP, and EBRT in case of subsequent disease progression. Currently, focal therapy in CAP is more a concept than a treatment option. There is not even a clear definition of *focal therapy* because it comprises hemi ablation, three-quarter ablation, index-lesion ablation, and true lesion plus margin focal ablation of CAP. Initial patient series are promising but patient numbers are still to small and follow-up to short to draw any valid conclusions about the oncologic efficacy and advantage of focal therapy in comparison with full ablation treatment options or active surveillance[10]. Due to its highly experimental character, focal therapy in CAP should only be performed within well-designed studies. Beside oncologic safety, our interest should focus on the true benefit for quality of life when compared with both active surveillance and ablative treatment. A number of recruiting trials focus on side effects following focal or hemi ablation treatment in CAP patients. It is expected that in the near future, there will be more valuable data on quality of life following focal HIFU treatment than for full-gland ablation.

Although HIFU is an emerging technology in CAP treatment, the review by Warmuth et al presents a disillusioning picture of the quality of current HIFU data. What can we expect from scientific work on HIFU for the next years? Concerning full-gland ablation, we expect data from the ongoing comparative trials as well as the first real "long-term" data to emerge from multicentre series. Parallel to that, there will be early results from focal therapy trials. Because most of the current studies use a hemi ablation protocol, further technical advances are expected with improved CAP imaging, allowing for real focal therapy, even in multifocal-pattern CAP.

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Bangladesh Journal of Urology

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