Utilization of Focal Therapy for Patients Discontinuing Active Surveillance: Recommendations of an International Delphi Consensus from the Focal Therapy Society

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Abstract

INTRODUCTION: With the advancement of imaging technology, focal therapy (FT) has been gaining acceptance for the treatment of select patients with localized prostate cancer (PCa). We aim to provide details of a formal physician consensus on the utilization of FT for patients with PCa who are discontinuing active surveillance (AS).

METHODS: A four-stage Delphi consensus of 91 international experts in PCa and FT was conducted. Consensus was defined as agreement by ≥80% of physicians. An in-person meeting was attended by 17 panelists to formulate the consensus statement.

RESULTS: The response rate was 62%, 62% and 54% for rounds 1 to 3, respectively. Consensus was obtained in 13 of 15 domains. Respondents confirmed that there is a role for FT in men discontinuing AS (48% strongly agree, 39% agree). The benefit of FT over radical therapy for men coming off AS are: FT is less invasive (91%), has a greater likelihood to preserve erectile function (91%), has a greater likelihood to preserve urinary continence (91%), has less side effects (86%) and has early recovery post-treatment (80%). Patients will need to undergo mpMRI of the prostate and/or a saturation biopsy to determine if they are potential candidates for FT.

CONCLUSIONS: FT can be offered to men coming off AS between the age of 60-80 with grade group 2 localized cancer and a PSA <10 ng/ml. This consensus from a multi-disciplinary, multi-institutional, international expert panel in FT provides a contemporary insight utilizing FT for PCa in select patients who are discontinuing AS.
Introduction

Low grade localized prostate cancer (PCa) has a long natural course, has no metastatic potential,\textsuperscript{1,2} and is widely considered to be clinically insignificant.\textsuperscript{3,4} The growth rate of many of these cancers is extremely slow.\textsuperscript{5} Active surveillance (AS) is the standard of care for these men.\textsuperscript{6,7} In fact, multiple prospective phase 2 trials with follow up ranging from 10 to 29 years have shown cancer-specific survival rates comparable to series of patients treated with radical prostatectomy.\textsuperscript{8-11} Over time, some of these men are later reclassified to a higher risk disease category (usually grade progression) and eventually receive definitive therapy. These therapies are associated with well-known quality-of-life side-effects.

In recent years, advancements in imaging and targeted biopsy have created the opportunity for an informed implementation of focal treatment of PCa.\textsuperscript{12-14} Focal therapy (FT), or partial gland ablation entails applying some form of energy to the area of the prostate that harbors clinically significant cancer, with the goal of achieving less morbidity yet similar cancer control compared to whole-gland approaches.\textsuperscript{15-18} However, there is no evidence in the literature specifically pertaining to FT for men discontinuing AS.

In topics where there is limited or little high quality evidence, the development of expert consensus is a valuable approach to address specific topics where opinion from experts become important.\textsuperscript{19} The Delphi method was conceived in the 1950s by Olaf Helmer and Norman Dalkey to allow experts to arrive at a group consensus by providing them with multiple rounds of questionnaires, as well as the group’s response before each subsequent round. In this report, we sought to develop a contemporary expert consensus on the utilization of FT for appropriate men with PCa who are discontinuing AS.
Methods

An online Delphi survey among FT experts around the world was conducted. The web-based questionnaire was constructed by the use of Survey Monkey (www.surveymonkey.com, San Mateo, California, USA) that was accessed between January 1st, 2020 and February 15th, 2020.

The participants were sent the questionnaire electronically in three consecutive rounds. At each subsequent round, the aggregate results of the prior round were presented anonymously, and the participants allowed to modify their responses. Feedback and comments provided by experts were utilized to adjust/refine existing questions or explore controversial topics in greater depth. The final questionnaire is listed in Appendix 1. Achieving consensus was defined by having ≥80% agreement for each question.  

Participant selection

FT experts were identified and invited to participate based on prior presentations at plenary sessions at previous international FT symposium conferences, clinical and research interest in PCa by means of reputation, authorship on review topics or peer recommendation (Appendix 2). These physicians have expertise in imaging, targeting, focal therapy or a combination of the above. The experts were selected to represent professional groups that directly influence patient care and would benefit from clinical practice guidelines. Patients, nurses and administrators were not included as participants as the goal of the study was to develop
standards of care based on a clinician’s perspective. The participants consisted of urologic surgeons, radiologists, interventional radiologists and radiation oncologist.

**Systematic review of the literature**

A systematic review of the literature was performed to identify best practice evidence for clinical guidelines development. A PubMed search was performed up to January 2\textsuperscript{nd} 2020. The detailed search terms, filters and exclusions are presented in Figure 1. The search strategy consisted of combined headings and keywords for “prostate cancer” and “active surveillance” and “focal therapy” (see textbox in Figure 1). Reference lists from included publications were also screened to identify additional papers.

**Round 1**

The first round of the Delphi consensus contained 27 questions. Checkboxes were used rather than multiple choices to allow the selection of more than one answer. A 5-point Likert scale was utilized rather than ‘yes-no’ responses to evaluate the participant’s level of agreement. Experts were also given the opportunity to provide comments and suggest additional items that may not have been included when developing the initial list of statements. The intention of round one was to address any redundancies or issues regarding comprehension or syntax of each statement and to allow the experts to provide feedback to improve the survey. Statements not meeting 80% agreement were modified according to the feedback provided by the participants and redistributed for round 2.
Round 2

The list of statements not meeting consensus from round 1 was emailed to all participants. In round 2, the experts were presented with a similar voting method to round 1, except that each question began with the group scores from round 1. Hence, the experts could reflect upon the group results and change/modify/take into account their peers answer accordingly, while preserving the anonymity of their/all responses. Final responses were analyzed as described for round 1, and statements not achieving consensus were retained for round 3.

Round 3

The list of statements not achieving consensus from round 2 was emailed to all participants. Similar to round 2, the experts were presented with the group results and allowed to change/modify their answer accordingly. Final responses were analyzed similar to previous rounds and statements not achieving consensus were retained for round 4.

Round 4

Round 4 consisted of a face-to-face meeting that occurred at the 12th International Symposium of Focal Therapy and Imaging in Prostate and Kidney Cancer in Washington DC on February 10th, 2020. Anonymity was not retained for round 4 as voting occurred using a show of hands. The face-to-face meeting was mediated by a meeting chair (WPT) and the panel members discussed the remaining statements until agreement was achieved to retain, eliminate or modify the statements from the final guideline document. The meeting was recorded for documentation purposes.

Statistical Analysis
Data are presented as percentages. Data was analyzed using SurveyMonkey Inc platform at www.surveymonkey.com.
Results

Participant selection

Ninety-one experts were invited to participate in the Delphi consensus. The response rate for round 1, round 2 and round 3 was 56 (62%), 56 (62%) and 49 (54%) respectively. A total of 17 experts attended the face-to-face meeting (Appendix 2).

Systematic review of the literature

The literature search was performed to identify best practice evidence of clinical practice guidelines for the utilization of FT for patients discontinuing AS. The search identified 80 publications. Of these, 18 were selected based on title and abstracts. None were provided to the core group given there is no published literature pertaining to data on utilization of FT for men discontinuing AS (Figure 1).

Results from the consensus project

Demographics of respondents

Checkboxes were used for the demographics portion of the survey and multiple selections were possible. Therefore, total responses could exceed 100%. Forty (71%) of participants self-identified as a urologic oncologist, followed by 11 (20%) identifying as a general urologist and 7 (13%) identifying as an endourologist and/or radiologist, respectively (Table 1). Fifty-one (91%) participants practice in an academic setting followed by 5 (9%) identifying as practicing in a private setting. Forty-six (82%) participants practice in a major city (>750k population) while 5 (9%) participants work in a large city (500k – 750k population) and 5 (9%) participants work in a
suburban setting (100 – 500k population), respectively. Forty-four (79%) of participants perform laparoscopic/robotic prostatectomies, followed by cryoablation of the prostate, n= 25 (45%), brachytherapy, n=24 (43%) and HIFU, n=41 (41%) Table 1.

Role of FT in men discontinuing AS

The experts agree that there may be a role for FT in men discontinuing AS (48% strongly agree, 39% agree). The respondents’ rationale for recommending FT over radical therapy, in select men discontinuing AS, was that FT is less invasive (91%), has a greater likelihood of preserving erectile function (91%), has a greater likelihood of preserving urinary continence (91%), has less side effects (86%) and has early recovery post-treatment (80%). Given the appropriate clinical circumstances and assuming a biopsy proven MRI-targetable lesion, the experts agreed that a physician may consider FT when upgrading from grade group 1 to 2 occurs on fusion biopsy. The group agreed that FT for men discontinuing AS should be considered between age 60 and 80 (88% selected 60-69 and 89% selected 70-80).

Workup prior to FT

There was no consensus pertaining to PSA criteria that might affect the decision to recommend FT. The panel recommended that a PSA increase would prompt re-interrogation of the prostate, but not prompt a decision to perform FT (100%). The panel agreed that a molecular biomarker indicating high risk of adverse pathology might influence the physician to re-interrogate the prostate, but not necessarily prompt a decision to perform FT (100%).
In terms of the type of biopsy technique used to evaluate a patient currently on AS who is considering FT, the group agreed that the patient should undergo an MRI targeted biopsy plus 12 core systematic biopsy (88%). A consensus could not be reached pertaining to a metastatic workup, but the panel voted (round 4) that a metastatic workup is not required for patients with low risk and intermediate favorable risk based on the NCCN guidelines (100%).

If a patient is unable to undergo a mpMRI, the group agreed that a 3D mapping biopsy of the prostate that demonstrates a reasonably localized tumor burden based on pathological analysis is sufficient for FT (85%). In a patient who does not have an MRI-visible lesion, the group agreed that they would not offer the patient FT if the patient only underwent a 12-core random biopsy (80%).

**Focal therapy margin**

For the scenario-based questions, Figure 2A shows a single grade group 2 lesion in the prostate, away from the neurovascular bundle; Figure 2B shows grade group 1 and 2 lesions in the anterior prostate, away from the neurovascular bundles; Figure 2C shows two grade group 2 lesions, one being adjacent to the neurovascular bundle and the other in the anterior prostate. The group agreed that FT could be offered to Figure 2A and 2B. However, the group could not come to a consensus on the ideal template for FT for clinical scenarios illustrated by both/either Figure 2A and 2B. There was no consensus if FT should be offered for the clinical scenario in Figure 2C. However, the panel decided that given the multi-focality of the disease, this would not represent an ideal candidate for FT (100%).
Seven questions were omitted as they were part of a multiple-step question for the scenario-based questions. These questions pertained to the type of metastatic workup prior to FT, and ablation template for different scenarios that the panel voted as not representing ideal candidates for FT. A summary of the consensus statements is shown on Table 2.
Discussion

With the improvement in imaging modalities for PCa, FT has been introduced as a novel treatment option for select men with localized PCa. However, the majority of FT trials included grade group 1 patients (who would be more appropriately managed with AS), and no study to date has evaluated the use of FT for men discontinuing AS.\textsuperscript{15, 25, 26} In this consensus, we aimed to explore the use of FT for men with PCa coming off AS. Most men on AS initially have grade group 1 or limited 2 disease. We found that the majority of participants agreed that there is a role for FT in this cohort in the appropriately-selected patient.

Participants of the survey agreed that a patient with a solitary Gleason 3+4 lesion (grade group 2) is the ideal candidate for FT and that most of these lesions can be safely and effectively ablated. However, there was no clear consensus on the ideal treatment template for such a lesion. In fact, even after the panel convened in person (round 4), we were unable to achieve a consensus on the ideal template for treatment. We believe this is because different energy sources result in different ablation margins. Also, FT provides the physician with the ability to customize a therapy plan based on the location, size and number of tumor(s) within the prostate. The panel also felt that patients with multiple clinically significant lesions (≥Grade group 2) that are not located within the anterior prostate are not ideal candidates for FT (Figure 2C).

Five questions did not achieve consensus during the first three rounds of the Delphi Consensus. The seventeen experts on the panel were able to achieve consensus for three of the questions. The panel strongly believed that PSA and the result of any biomarker should not influence the decision to perform FT in an absolute sense, but these markers should guide the
decision to undertake further evaluation. A biomarker result suggesting adverse pathology should prompt an mpMRI and eventually a fusion-guided biopsy and 12 core biopsy. The panel also agreed that no metastatic workup is required under usual circumstances in patients who are candidates for FT, given a metastatic workup is only warranted in patients with intermediate unfavorable or high risk cancer.\textsuperscript{24,27} Those patients displaying excessive risk should not be considered for FT in the primary setting as traditional management options would likely serve them better. The two questions that did not reach consensus were those regarding the ideal choice of templates for patients undergoing FT (Figure \textbf{2A and 2B}).

Two prior consensus addressed surveillance following FT.\textsuperscript{28,29} There was consensus that PSA does not currently offer any reliable, reproducible data in the follow-up after FT. Although the doubling time of PSA may be an important criterion predicting treatment failure, it does not represent a good parameter for biochemical recurrence. Tay et al performed a systematic review pertaining to surveillance after prostate FT and concluded that mpMRI should be performed at 3-6 months, 12-24 months and at 5 years after FT.\textsuperscript{30} They also suggested that targeted biopsy of the treated zone and any suspicious lesion seen on MRI should be performed at 3-6 months, and a systematic biopsy should be performed at 12-24 months and again at 5 years.\textsuperscript{30}

This consensus has several limitations and should be interpreted within its context. First, this was a selected group of clinicians interested in FT, which may reflect selection bias. The group’s opinion may not be representative of the larger medical community. The response rate for our consensus was between 54% and 64%. This response rate, although reasonable, limits the generalizability of the conclusions. The final consensus meeting was comprised of 17
experts and may not have represented the views of all 91 invitees. Finally, the repetition and reformulation of questions and answer choices by the project leaders may also incur bias, an inherent limitation of the Delphi method. Despite these limitations, this consensus reflects the opinion of a multi-disciplinary, global community with many members involved in traditional radical therapy for the treatment of prostate cancer. Moreover, this report reflects the position of the Focal Therapy Society and receives as such an official status.
Conclusion

FT in men with localized PCa discontinuing AS is gaining wider acceptance. This consensus report provides context and guidance that a minimally-invasive gland and function-preserving strategy should be considered as a potential next step. In the appropriate clinical context, PCa specialists should contemplate treating an image-targetable tumor(s) in these men rather than resorting to whole gland therapy with its attendant side effects. The advantages are an improved quality life. For men with GG 2 PCa whose mortality risk is low, this is an extremely appealing prospect, particularly to patients who may not require the most aggressive forms of treatment.
Table Legend:

Table 1: Demographics of physicians completing the survey
Table 2: Summary of consensus statements

Figure legend:

Figure 1: Search terms for literature review.
Figure 2A: MRI lesion and biopsy results for question 15 & 16
Figure 2B: MRI lesion and biopsy results for question 17 & 18
Figure 2C: MRI lesion and biopsy results for question 19

Appendix legend:

Appendix 1: Results of consensus statements.
Appendix 2: All registered participants for the Delphi Consensus.

Supplementary Figure legends:

Supplementary Figure 1: Ablation template for question 16.
Supplementary Figure 2: Ablation template for question 18.
Contribution

Contribution to the conception or design of the work: WPT, ARR, TJP

Acquisition of data: WPT, ARR, LK, RTG, ME, JFF, AKG, AEK, LSM, GM, DYS, AS, PRC, ISG, JFW, AHL, PAP, RSS, JR, TJP

Analysis of data: WPT

Interpretation of data: WPT, ARR, LK, RTG, ME, JFF, AKG, AEK, LSM, GM, DYS, AS, PRC, ISG, JFW, AHL, PAP, RSS, JR, TJP

Drafting of the manuscript: WPT

Revision of the manuscript: ARR, LK, RTG, ME, JFF, AKG, AEK, LSM, GM, DYS, AS, PRC, ISG, JFW, AHL, PAP, RSS, JR, TJP

Final approval of the manuscript: WPT, ARR, LK, RTG, ME, JFF, AKG, AEK, LSM, GM, DYS, AS, PRC, ISG, JFW, AHL, PAP, RSS, JR, TJP

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: WPT, ARR, LK, RTG, ME, JFF, AKG, AEK, LSM, GM, DYS, AS, PRC, ISG, JFW, AHL, PAP, RSS, JR, TJP
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