Urologic Oncology: Seminars and Original Investigations 37 (2019) 182.e1–182.e8

UROLOGIC ONCOLOGY

Clinical-Prostate cancer

Analyzing the current practice patterns and views among urologists regarding focal therapy for prostate cancer

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Received 24 July 2018; received in revised form 11 November 2018; accepted 19 November 2018

Abstract

Introduction and objective: Focal therapy (FT) for localized prostate cancer (CaP) has been shown to have encouraging short-term oncological outcomes, excellent preservation of functional outcomes and is increasing in popularity in urologic community. We aim to evaluate the preferences and practice trends among urologists regarding this treatment strategy.

Methods: A 20 item online questionnaire was designed to collect information on urologists' views and use of FT. The survey was sent to the members of the Endourological Society and the American Urological Association. Multivariate logistic regression analysis was done to determine predictors for utilization of FT.

Results: A total of 425 responses were received [American Urological Association: 319, Endourological Society: 106]. Mean age of respondents was 53(SD: 11.3) years. Although half of the respondents (50.8%) believed FT to be moderate to extremely beneficial in the treatment of CaP, only 24.2% (103) of the respondents currently utilize FT in their practice. Respondents who were fellowship trained in urologic oncology were more likely to consider FT to be at least moderately beneficial ($P < 0.001$). Surgeon's experience (greater than 15 years in urology practice) ($P = 0.025$) and seeing more than 10 patients with new CaP diagnosis per month ($P = 0.002$) were independent predictors of FT utilization for localized CaP. While the most common setting for utilization of FT was in patients with unilateral intermediate-risk (72.8%) CaP, a small percentage of respondents also used FT for patients with unilateral high-risk CaP and bilateral intermediate risk (21.4% and 10.7%, respectively). Most common reasons for not using FT were the lack of belief in 'index lesion theory' (63.2%), lack of experience (41.3%), lack of belief in FT's efficacy (41.1%), lack of infrastructure (35.8%), difficult salvage treatment in cases of recurrence (22.7%) and high cost (21.8%). About 57.6% would use FT more often in an office or outpatient setting if they had access to reliable and cost-effective options.

Conclusions: Only a quarter of our respondents utilize FT in their practice with surgeon's experience being the important independent predictor for using FT. Majority of respondents though consider FT to be beneficial in CaP management, would use it more often if provided more reliable and cost-effective options. Over time, experience and accessibility to reliable methods to perform FT may lead to further utilization of this novel treatment strategy.

Keywords: Prostate cancer; Focal therapy; Multiparametric MRI; Survey

1. Introduction

The widespread use of prostate-specific antigen screening has led to an earlier and increased diagnosis of low-risk prostate cancer (CaP) [1,2]. While urologists have increasingly been using active surveillance for very low-risk and low-risk disease, whole gland treatment (WGT) by means of radical prostatectomy and radiation therapy is still

Funding: This research was supported by the Intramural Research Program of the National Institutes of Health (NIH), National Cancer Institute, Center for Cancer Research, and the Center for Interventional Oncology. NIH and Philips Healthcare have a cooperative research and development agreement. NIH and Philips share intellectual property in the field.

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https://doi.org/10.1016/j.urolonc.2018.11.018
1078-1439/

widely used for high volume low-risk and low volume intermediate-risk CaP. However, the risk of CaP mortality in these populations is low [3,4]. These patients may ultimately receive WGT because of several reasons, including, but not limited to, concerns of the patient and physician, young patient age, and strong family history [3,5]. The radical treatment strategy in such patients has the potential of overtreatment and can lead to treatment related morbidity such as urinary and erectile issues.

Focal therapy (FT) for localized CaP is a treatment strategy which aims to destroy only the cancerous areas in prostate while preserving rest of the prostate with the aim of maintaining genitourinary function. It has been shown to have encouraging short-term oncological outcomes, excellent preservation of functional outcomes and is increasing in popularity in urologic community [6–8].

FT is based on the principle of targeting the "index lesion." The "index lesion" is defined as the most significant focus of tumor in the gland with the highest Gleason score and has been shown to be responsible for the cancer progression, and hence, treating this particular lesion may have the potential of accomplishing oncological outcomes similar to WGT [9,10]. FT in the oncological world has shown promising results in other various solid malignancies, but its use is limited in CaP due to inadequate results. In the kidney, there has been a transition from radical nephrectomy to nephron preserving surgery. Foreseeing a similar shift in CaP, FT is meticulously evaluated.

In our previous survey regarding multiparametric magnetic resonance imaging (MRI) and magnetic resonance (MR)-targeted biopsy, 27% of respondents utilized MR-targeted biopsy for localizing disease in FT candidates [11]. As there is debate surrounding the use of FT in CaP, we hope to evaluate the current status of FT in the urologic community further. To our knowledge, no previous study has gauged the utilization of FT in physicians' practice for CaP. In this study, we aim to evaluate the current beliefs, practice patterns, and viewpoints among urologists regarding utilization of FT for localized CaP.

2. Materials and methods

2.1. Survey instrument

A 20-item questionnaire was designed to collect demographic information and data on urologists' beliefs, practice patterns, and experience with using FT for localized CaP. The questionnaire was designed in a branching fashion such that respondents were taken to different follow-up questions based on how they responded to the previous question. Also, some questions allowed respondents to "select all that apply" in response to the question. Information was obtained on the respondents' age, practice type, geographical location, years in practice, fellowship training in urologic oncology, urological societies, number of CaP patients seen in a month, and use of FT for CaP in clinical practice. Respondents were also asked if they believed in index lesion theory as the basis for FT. Index lesion theory was defined "in the multifocal CaP, only the index lesion, the largest tumor focus with the highest grade, determines the prognosis."

2.2. Study design

A link to the survey was sent through e-mail to the members of Endourological Society (ES) and the American Urological Association (AUA). Approximately 3,000 members of AUA and 2,800 members of ES received requests for the study. As both the societies have heterogeneous member population (practicing physicians, research scientist, etc.), an unknown number of recipients qualified for the study, and therefore the response rate could not be accurately calculated. The responses were automatically and anonymously collected in a spreadsheet. The study was determined to be exempt from review by institutional review board by the Office of Human Subjects Research Protection at the National Institutes of Health.

2.3. Statistics

Data management was performed using Microsoft Excel version 2016 (Seattle, Washington). Statistical analysis was performed using STATA version 14.0 (StataCorp LP, College Station, TX). Pearson chi-square and Fisher's exact test were used to comparing proportions of categorical variables. Wilcoxon rank sum test was used to compare the distribution of continuous variables. Univariate and multivariate logistic regression models were performed to identify predictors for utilization of FT in practice. Respondent's age, practice type, oncology fellowship training, the number of CaP patients newly diagnosed per month, and the number of years in urology practice were used in regression analysis. Odds ratio (OR) with 95% confidence interval were calculated, and statistical significance was defined as $P < 0.05$.

3. Results

3.1. Respondent characteristics

A total of 425 responses were received which included 319 (75.1%) from AUA, and 106 (24.9%) from the ES. Characteristics of the respondents are shown in Table 1. Mean age of the respondents was 53.4 (SD 11.3) years, with 137 (32.5%) fellowship trained in urologic oncology, 223 (52.8%) with practice based in the US, and 182 (42.9%) practicing in an academic setting.

The majority of the US-based respondents tended to be practicing in a nonacademic setting) than in an academic setting (72.2% vs. 27.8%, $P < 0.001$). Respondents practicing in academic environment tended to be younger on average (51.2 years (SD 11.4) vs. 55.2 years (SD 10.9), $P < 0.001$) and more often were fellowship trained (66.2% vs.

Table 1
Characteristics of 425 survey respondents

	n (%)
Age (*n* = 425), mean (±SD), y	53.47 (11.31)
Society (*n* = 425)	
American Urological Association, *n* (%)	319 (75.1)
The Endourological Society, *n* (%)	106 (24.9)
Practice type (*n* = 424)	
Academic, *n* (%)	182 (42.9)
Nonacademic, *n* (%)	242 (57.1)
Practice based in the United States (*n* = 422)	
No, *n* (%)	199 (47.2)
Yes, *n* (%)	223 (52.8)
Years in practice (*n* = 424)	
0−5, *n* (%)	33 (7.8)
6−10, *n* (%)	53 (12.5)
11−15, *n* (%)	61 (14.4)
>15, *n* (%)	277 (65.3)
Fellowship trained in urologic oncology (*n* = 421)	
No, *n* (%)	284 (67.5)
Yes, *n* (%)	137 (32.5)
No. of patients seen monthly with newly diagnosed prostate cancer (*n* = 423)	
1−5, *n* (%)	173 (41)
6−10, *n* (%)	154 (36.4)
11−15, *n* (%)	48 (11.3)
>15, *n* (%)	48 (11.3)

33.8%, $P < 0.001$) than those practicing in a nonacademic setting.

3.2. Survey responses

Participants' responses to survey questions are presented in Table 2. Half of the respondents believed FT to be at least moderately beneficial for the treatment of localized CaP. Academic urologists were more likely to consider FT beneficial (59% vs. 44%, $P = 0.034$). Fellowship training or the number of years in urology practice had no relation to believing how beneficial FT was ($P = 0.183$ and $P = 0.934$, respectively).

In total, 45% of participants believed in the index lesion theory. Urologists in the academic setting were more likely to believe in the index lesion theory (53.8% vs. 38.6%, $P = 0.002$). There was no significant difference in the belief in index lesion theory among urologic oncology fellowship trained individuals and nonfellowship trained individuals (46% vs. 44.5%, $P = 0.830$). Furthermore, US-based physicians were less inclined to believe the index lesion theory (40.8% vs. 50.7%, $P = 0.04$) than the overseas physicians.

Overall, 24% participants utilized FT in their practice (Table 2). Not surprisingly, respondents who believed in the index theory tended to utilize FT more than skeptics of the theory (40.1% vs. 11.2%, $P < 0.001$). There was no significant difference in FT utilization among academic or nonacademic physicians (26.9% vs. 21.9%, $P = 0.23$). Urologists who were fellowship trained in oncology were slightly more inclined to utilize FT compared with nonfellowship trained physicians (29.2% vs. 21.8, $P = 0.09$). Furthermore, the majority of physicians who employed FT were in clinical practice for greater than 15 years (76.7% vs. 23.3%, $P = 0.005$). While the most common setting for utilization of FT was in patients with unilateral intermediate risk CaP (72.8%), a minor percentage of respondents also used FT for patients with bilateral intermediate-risk and unilateral high-risk CaP (10.6% and 21.3%, respectively; Fig. 1). Majority respondents preferred to use multiparametric MRI (mp-MRI) to identify candidates for FT. mp-MRI was used either with systemic transrectal ultrasound (TRUS) biopsy (32%) or MRI-TRUS fusion biopsy (32%).

The most common FT modality used by physicians was cryoablation (56%) followed by high-intensity focused ultrasound (HIFU) (44.6%; Fig. 1). Urinary retention and erectile dysfunction were the 2 most common postoperative complications reported by the 67% and 28% of the respondents (Fig. 1). Among respondents who do not utilize FT, 3 most common reasons for not using FT were the lack of belief in "index lesion theory" (63%) followed by the lack of experience (41.4%) and lack in the belief of its efficacy (41.1%; Fig. 1).

3.3. Prediction of focal therapy use

The results of the logistic regression analyses are shown in Table 3. On both univariate and multivariate logistic regression, physician's experience (more than 15 years in urology practice; OR 2.43 [1.11−5.26], $P = 0.025$) and seeing more than 10 patients with new CaP diagnosis per month (OR 2.32 [1.36−3.94], $P = 0.002$) were independent predictors of FT utilization for localized CaP in practice.

Lastly, more than half of the respondents (57.8%) indicated that they would utilize FT more often if they had access to reliable and cost-effective methods. Furthermore, 52% of respondents believed that using navigation and treatment planning tools would improve FT outcomes.

4. Discussion

Numerous studies have established that the majority of CaP cases are multifocal in origin [12−16]. The multifocality concept is the biggest obstacle to the implementation of FT. However, as described earlier, there is evidence that "index lesion" characteristics can predict the oncological outcomes (index lesion theory) [17,18]. Ohori et al. ascertained "index lesion" makes up for up to 80% of the cancer burden [19]. More recently, Liu et al. from Johns Hopkins, implementing copy number analysis, proposed a monoclonal origin of lethal metastatic CaP [20]. Interestingly in our survey, overall 45% of physicians believed in the "index lesion" theory. Based on the evolving index lesion theory, FT is currently increasingly used and evaluated in the urologic oncology world. It will be exciting to see "index lesion" theory development in the future.

Table 2
Participant's responses to survey questions

	n (%)
How beneficial is Focal therapy for CaP? (*n* = 421)	
No benefit at all	63 (15)
Slightly beneficial	144 (34.2)
Moderately beneficial	130 (30.9)
Very beneficial	68 (16.1)
Extremely beneficial	16 (3.8)
Belief in "index lesion theory"? (*n* = 424)	
No	232 (54.7)
Yes	192 (45.3)
Use focal therapy for CaP? (*n* = 425)	
No	322 (75.8)
Yes	103 (24.2)
If no, reasons for not using focal therapy?[a] (*n* = 321)	
Index lesion theory is not established	203 (63.2)
Lack of experience	133 (41.4)
Lack of efficacy of focal therapy	132 (41.1)
Lack of infrastructure	115 (35.8)
Salvage treatment is challenging in case of recurrence	73 (22.7)
Cost	70 (21.8)
If yes, what set of prostate cancer patients are preferred?[a] (*n* =103)	
Unilateral low risk (Gleason score 6)	68(66)
Bilateral low risk as long as urethra and one neurovascular bundle are preserved (Gleason score 6)	27(26.2)
Unilateral intermediate risk (Gleason score 7)	75(72.8)
Bilateral intermediate risk as long as urethra and one neurovascular bundle are preserved (Gleason score 7)	11(10.7)
Unilateral high risk (Gleason score >7)	22(21.4)
If yes, how are CaP focal therapy candidate identified? (*n* = 103)	
Based on systematic transrectal ultrasound (TRUS) biopsy only	11(10.7)
Multiparametric MRI (mp-MRI) and systematic TRUS biopsy	33(32)
Multiparametric MRI (mp-MRI) followed by MRI-TRUS fusion biopsy	33(32)
Template prostate mapping biopsies with or without Multiparametric MRI	26(25.2)
If yes, what modality?[a] (*n* = 103)	
Cryoablation	58(56.3)
High-intensity focal ultrasound (HIFU)	46(44.7)
Electroporation	13(12.6)
Laser ablation	6(5.8)
Photodynamic therapy	6(5.8)
Watervapor therapy	0(0)
Brachytherapy	2(1.9)
Radiofrequency	1(1)
If yes, how many times per year? (*n* = 101)	
1−5 patients per year	54(53.5)
5−10 patients per year	14(13.9)
10−15 patients per year	18(17.8)
>15 patients per year	15(14.9)
If yes, what complications are commonly encountered?[a] (*n* = 64)	
Urinary retention	43(67.2)
Urethral stricture	8(12.5)
Urinary incontinence	6(9.4)
Erectile dysfunction	18(28.1)
Rectal complications—perineal pain, rectal bleeding or rectourethral fistula	6(9.4)
If yes, how do you follow-up a patient post focal therapy? (*n* = 102)	
Prostate-specific antigen/ PSA kinetics	25(24.5)
mp-MRI followed by targeted biopsy only if there is a suspicious lesion	31(30.4)
Protocol biopsy at set intervals with or without prior mp-MRI	46(45.1)
If yes, do you attempt focal therapy for biopsy proven recurrent prostate cancer post focal therapy? (*n* = 101)	
Yes	59(58.4)
No	43(42.6)
Would use focal therapy more often if had access to a reliable and cost-effective way to perform focal therapy (*n* = 422)	
Yes	244 (57.8)
No	178 (42.2)
Believe that navigation tools and treatment planning tools can improve focal therapy outcomes? (*n* = 425)	
Yes	223 (52.5)
No	40 (9.4)
Maybe	162 (38.1)

CaP = prostate cancer.
[a] Select all that apply question.

Table 3
Logistic regression analysis for utilization of focal therapy

Variable	Use of focal therapy			
	Univariate OR [CI]	*P* value	Multivariate OR [CI]	*P* value
Age	1.02 [1.00–1.04]	0.046	1.00 [.97–1.03]	0.895
Practice type				
Nonacademic (reference)	1	–	1	–
Academic	1.31 [.84–2.05]	0.232	1.24 [.74–2.09]	0.408
Fellowship trained	1.48 [.93–2.34]	0.099	1.23 [.73–2.08]	0.433
US based practice	0.76 [.48–1.18]	0.218	0.93 [.56–1.54]	0.782
Years in practice (post residency)				
0–15(reference)	1	–	1	–
>15	2.04 [1.23–3.40]	**0.006**	2.43 [1.11–5.26]	**0.025**
No. of newly diagnosed CaP patients seen per month				
0–10 (reference)				
>10	2.18 [1.33–3.58]	**0.002**	2.32 [1.36–3.94]	**0.002**

CI = 95% confidence interval; OR = odds ratio.

Valerio et al.'s systemic review demonstrated that the majority of CaP patients treated with FT were men with low-risk and intermediate-risk disease [21]. Physicians utilizing FT in our survey had very similar selection criteria and used it most often for unilateral low- and intermediate-risk CaP patients.

In our survey, of the physicians utilizing FT, as much as two-thirds employed mp-MRI either followed by TRUS biopsy or MR targeted biopsy as prediagnostic interventions. Only a minority were selecting FT candidates based on TRUS biopsy alone. Prostate mp-MRI and MR-targeted biopsy have lately been recognized to precisely localize the index lesion [22,23]. Studies have proven mp-MRI's excellent diagnostic utility especially in clinically significant CaP (>0.5 cm^3 volume) [24–26]. Remarkably, Villers et al. demonstrated mp-MRI's excellent cancer localizing capability and also negative predictive value as high as 95% for clinically significant CaP [27]. An international Delphi consensus statement demonstrated a high level of agreement (92%) that mp-MRI is a standard imaging modality for patient selection for FT. Further, it described that patients with tumor foci <1.5 ml on mp-MRI of the prostate are advisable for FT [28,29]. The link between mp-MRI and FT may result in increased FT usage and confidence as the mp-MRI adoption increases. Though there is a clear link in these technologies, the most significant obstacle to FT adoption is a paucity of long-term beneficial evidence, as described by this survey. Indeed, large-scale favorable results and easier access to infrastructure looks to be critical for overall FT adoption. However, this is a rather tall order since FT must prove to have lower morbidity and noninferior oncologic outcomes than radical therapy.

In the last 2 decades, there has been a gradual increase in available therapy modalities. The application of each modality has been based on the tumor location. The 2 most common modalities used by the respondents were HIFU and cryoablation. This trend is not surprising since these 2 technologies are relatively mature modalities and have the most longitudinal data available. Based on the existing literature, focal cryotherapy seems to result in acceptable preliminary oncological outcomes with favorable morbidity profiles compared with radical treatment options [6,7]. Similarly, the efficacy rates for focal HIFU have been reported between 78% and 95% [30]. Finally, there are several newer focal modalities (Laser ablation, photodynamic therapy, etc.) that have entered early-phase clinical trials and various are still under active investigation to be used clinically. No randomized trials have shown that one modality is superior to another.

The most common complications post-FT per respondents in our survey was urinary retention and erectile dysfunction. To date, continence data and urinary symptoms after FT have not been reported universally. However, the limited evidence suggests that FT results in better urinary function compared to radical treatment options. Valerio et al. [21] identified complications like urinary retention and urinary infection in only 0% to 17% of total cases undergoing FT. Moreover, the limited literature suggests no significant difference between the complication rates between each of the FT modalities [31].

Respondents who were urologic oncology fellowship trained and more experienced tended to utilize FT in their practice. The regression analysis determined that being in practice for more than 15 years and diagnosing more than 10 CaP patients per month predicted utilization of FT. Managing more CaP patients may require being able to offer a variety of treatments. Interestingly, more than half of the participants endorsed using FT if they had better infrastructure and access to a cost-effective method. Hence, we believe as the FT technology advances further, we can anticipate its cost reduction and additional utilization in both smaller and larger centers.

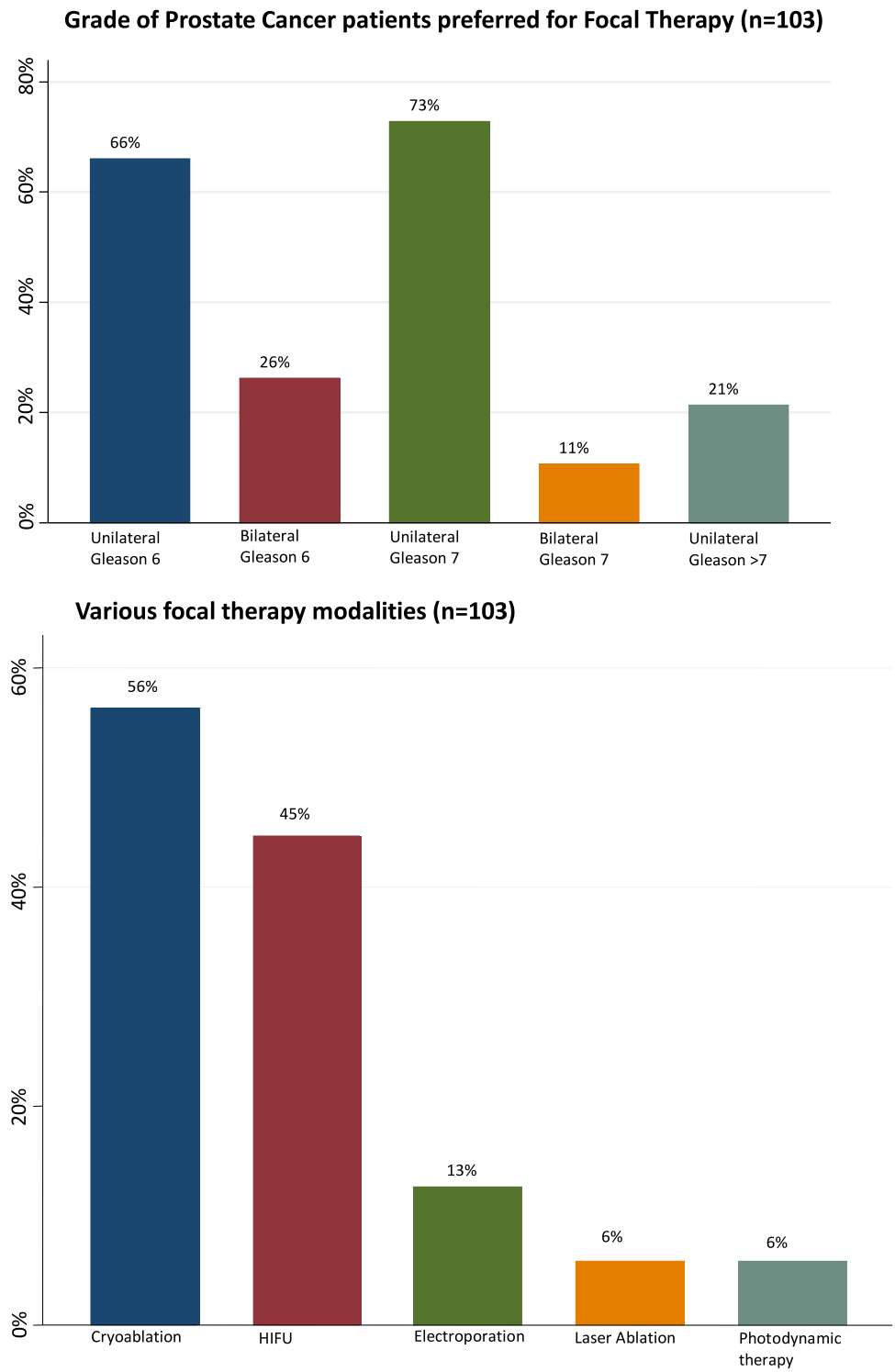

Fig. 1. Practice patterns for focal therapy.

The results of this study should be interpreted with limitations in mind, the first being the survey design. As discussed in the methods section, we are unable to determine the exact response rate, as well as the characteristics of those who did not respond to the survey. Those who are fellowship trained or those who are at academic centers may be more likely to complete the survey. The low response rate is a limitation of this study. Thus, this study is subject to a degree of respondent bias since conceivably, those who are more familiar with FT or those more likely to use FT are more likely to submit their opinions. With the potential for a nonrandom sample of respondents, the degree of

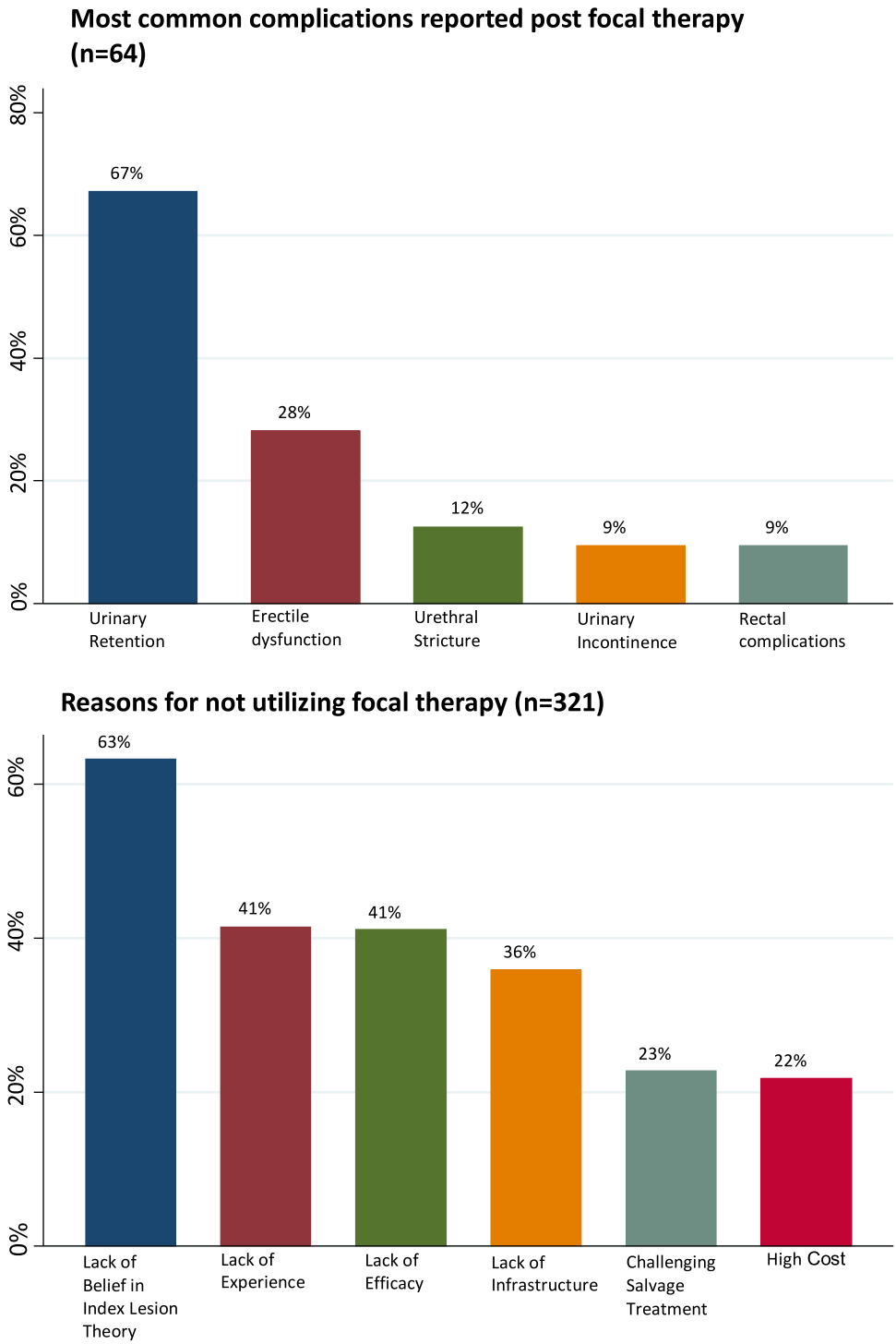

Fig. 1. Continued.

generalizability to all urologists is tempered. Nevertheless, this study provides valuable information about the physicians' psyche regarding FT utilization for CaP.

5. Conclusions

By current opinion, the usage of FT is supported for select men with low- and intermediate-risk CaP. There are many obstacles, including the lack of long-term evidence, infrastructure, and cost-effective access, which prevent more extensive implementation of FT. Index lesion theory has been crucial in the adoption and implementation of FT in the urology world. Cryoablation and HIFU and the most common modalities among those who use FT, and mp-MRI is frequently used in combination with FT. As this is an evolving field,

continuing survey studies will capture the change opinions and usage of FT.

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