Best Practice Policy Statement on

Cryosurgery for the Treatment of Localized Prostate Cancer

Change Notice: Any information related to Prostate-Specific Antigen (PSA) in the following guideline may have been revised in the American Urological Association's (AUA) *PSA Best Practice Statement: 2009 Update.* In the case of any discrepency in recommendations between guidelines pertaining to PSA, please refer to the AUA's *PSA Best Practice Statement: 2009 Update* for the latest AUA recommendation regarding PSA testing.

Panel Members:
Richard J. Babaian, MD, Chair
Bryan Donnelly, MD, Facilitator
Duke Bahn, MD
John G. Baust, PhD
Martin Dineen, MD
David Ellis, MD
Aaron Katz, MD
Louis Pisters, MD
Daniel Rukstalis, MD
Katsuto Shinohara, MD
J. Brantley Thrasher, MD

Panel Managers:
Kirsten Aquino
Judy Goldfarb

AUA Staff:
Heddy Hubbard, PhD
Edith M. Budd
Michael Folmer
Katherine Moore
Kadiatu Kebe

Medical Writing Assistance:
Diann Glickman, PharmD

American Urological Association
Education and Research, Inc.

Abbreviations and Acronyms

ASTRO = American Society for Therapeutic Radiology and Oncology

AUA = American Urological Association

BPS = Best Practice Statement

CN/P = cryoneedle/cryoprobe placement

EBRT = external beam radiation therapy

ED = erectile dysfunction

HRQL = health-related quality of life

PGC = Practice Guidelines Committee

PSA = prostate-specific antigen

RP = radical prostatectomy

SV = seminal vesicle

TRUS = transrectal ultrasound

TUR = transurethral resection

U. S. = United States

Part I

Introduction

The protracted natural history of clinically localized prostate cancer has confounded the development of a national consensus regarding the optimal treatment for this disease. In the American Urological Association's (AUA) 2007 *Guideline for the Management of Clinically Localized Prostate Cancer: 2007 Update*, multiple treatment modalities are considered as options.[1] This conundrum is further complicated by stage migration and lead time bias, both associated with prostate specific antigen (PSA)-based early detection strategies and the resultant increase in the detection of small volume clinically localized cancers.[2] Since the majority of men currently diagnosed with prostate cancer are likely to have the disease eradicated by one of several treatment modalities, the clinical focus on health related quality of life(HRQL) associated with treatment has intensified.[3] There are no published long-term data on the efficacy of cryosurgery on metastasis-free, prostate cancer-specific, or overall survival as there are with other more established forms of therapy; however, several large, single institution experiences, a pooled analysis, and several prospective evaluation studies report the efficacy and morbidity of cryosurgery of the prostate.[4-7] Additionally, prostate cryosurgery has been found to result in acceptable HRQL-based outcomes with a reduced cost when compared to other local therapeutic options.[8,9] Short-term PSA relapse-free survival outcomes following cryoablation of the entire prostate comparable to radiation therapy in men with intermediate- and high-risk disease have been reported.[4,7,10-13] Biochemical-free survival comparisons between radical prostatectomy (RP) and other nonextirpative therapies are difficult since the definitions for success are different.

The inherent treatment planning flexibility of cryosurgery lends itself to a targeted sub-total gland ablation approach for men with low-risk and/or small-volume cancers.[14]

Methodology

As noted in the AUA *Guideline for the Management of Clinically Localized Prostate Cancer: 2007 Update*[1], insufficient information was available to include cryosurgery in data meta-analyses. As such, the AUA convened a Panel (Appendix 1) to develop a Best Practice Statement (BPS) addressing the use of cryosurgery for the treatment of localized prostate cancer. A BPS uses published data in concert with expert opinion, but does not employ formal meta-analysis of the literature. A Medline search was performed using the Medical Subject Headings (MeSH) index headings "prostate cancer," and "cryosurgery," "cryotherapy," and "cryoablation," from 2000 through 2008. Publications were selected for review by the Panel members. The Panel formulated recommendations based on review of all material and the Panel members' expert opinions and experience which includes the treatment of several thousands of patients. Recommendations presented herein were achieved through a consensus process and may not reflect a unanimous decision by the Panel members. Levels of evidence were assigned based on the recommendations of the U.S. Preventive Services Task Force (Appendix 2).[15]

This document was submitted for peer review, and comments from all 19 responding physicians and researchers were considered by the Panel in making revisions. The revised document was submitted for a second peer review, and responses from all 21 responding physicians and researchers were considered by the Panel when making final revisions to the document. The final document was submitted to the AUA Practice Guideline Committee and Board of Directors for approval.

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Historical Development and Technological Advances

Some of the earliest reports of cryotherapy date back to the 19th century, when cervical and breast cancers were treated with a crude salt and ice mixture resulting in reduction of tumor volumes in some patients and improvement in local control.[16] In 1961, Cooper and Lee[17] developed the first cryotherapy probe system (Appendix 3), involving the circulation of liquid nitrogen through a closed metal tube placed in direct contact with the target tissue.[16] These early liquid-nitrogen probes, which allowed rapid freezing of tissue to -200°C, led to the nitrogen-based prostate cryosurgical procedures performed in the 1960s and 1970s. Soanes and Flocks and others used liquid-nitrogen probes placed either transurethrally or via an open perineal incision to treat both benign prostatic hyperplasia (BPH) and prostate cancer.[18,19] Notably, the freezing process was monitored by direct visualization, which was unreliable and resulted in an unacceptably high complication rate.[20,21] Dreaded complications such as total urinary incontinence, rectourethral fistulas, urethral sloughing, and stricture were common.

In the early 1990s, adoption of urethral warmers[22] was essential in reducing the risk of urethral sloughing[23], and the implementation of transrectal ultrasound (TRUS)[22] for percutaneous probe placement significantly advanced technology. Ice-ball formation could now be monitored to ensure complete prostate ablation while reducing damage to adjacent tissue. On ultrasound imaging, the edge of the frozen tissue appears as a hyperechoic rim with acoustic shadowing.[22,24] The use of thermocouple devices introduced in the mid 1990s allowed the surgeon to determine the extent of cell damage and served as an endpoint to the freezing cycle when temperatures <-40°C were reached. Thermocouples record when lethal temperatures are achieved in the prostate and when nondestructive, warmer temperatures are maintained in sensitive adjacent structures such as the rectum (Denonvilliers' fascia) and external sphincter.[25] Next, a multiprobe

system, allowing percutaneous placement under TRUS guidance, was developed. These probes were 3 mm in diameter, requiring dilation of the tract for placement.

Another technological advancement occurred when the original liquid nitrogen technology was replaced by argon-based cryosurgery in which pressurized argon gas allows for rapid temperature drops by the free expansion of gas (Joule-Thompson effect). Real-time control of ice-ball formation improved the precision of tissue ablation and further minimized harm to adjacent tissue. The transition to gas also permitted the advent of systems using thin (2.4 mm diameter) or ultrathin (17-gauge; 1.5 mm diameter) cryoneedles or smaller (2.4 mm diameter) cryoprobes that could be percutaneously passed through a brachytherapy-like template[25] or freehand. Separate skin incisions and tract dilation were no longer necessary.[26,27] Helium gas, which warms when it expands, provided an active warming capability that was not available in the liquid-nitrogen systems.[28] The introduction of pinpoint thermocouples, another feature of argon-based cryosurgery systems, further reduced procedural complications.[28] In addition to the smaller needle system, computer software was developed that has the ability to generate preoperative isotherm maps based on theoretical cryoneedle placements. This latest strategy for ablation allows the surgeon to plan needle placement so as to best target diseased tissue and avoid damaging important structures.

The operative time averages two hours, and the majority of the cases can be performed as outpatient procedures with either a Foley or suprapubic catheter placed for 5 to 14 days. With the aforementioned technological advances, there has been a significant reduction in overall side effects, including urinary incontinence, rectal pain, and urethral sloughing.[23]

In summary, a review of the historical evolution of cryosurgery provides two overriding messages, the first being that there is evidence of therapeutic benefit, and the second, that treatment-associated morbidity has been reduced as technological refinements have emerged.

Scientific Background

Clinically, cryosurgical procedures are grounded on well-recognized scientific principles supporting physician-managed destruction of clinically-localized tumors of the prostate.[29-31] When performed with multiprobe devices and advanced imaging techniques, cryosurgery has yielded effective short-term biochemical disease free results in the treatment of prostate adenocarcinoma.[4,7,12] Prostate geometry dictates cryoneedle/cryoprobe (CN/P) placement: CN/Ps are placed to support thermal homogeneity at approximately -40°C throughout the prostate. Following ultrasound-guided placement of CN/P, the physician directs freezing from anterior to posterior in the gland. This sequencing supports clear visualization and control of the ablative process.[32,33] Other CN/P placement strategies have also been reported showing similar ablative performance.[4,10,14]

Cryosurgery is a thermal therapy in that it extracts heat (thermal energy) from the targeted tissue resulting in a series of destructive effects. It is long recognized that the tissue response from cold injury, which can range from inflammation to total destruction, depends on the severity of freezing. The lesion created by freezing is characterized by coagulation necrosis in the central region with a surrounding, relatively thin, peripheral region in which cell death is apparent.[34,35]

There are two scientific principles that underlie successful cryodestruction of tissue. The first relates to the cellular responses to freezing that induce cell death, including freeze rupture,

necrosis and apoptosis. "Freeze rupture" is the term used to describe the cascade of events that leads to cell stress and death. With the onset of ice formation, water is "extracted" from the extracellular solution as pure crystalline ice, leaving an increasingly hyperosmotic solution. This hyperosmotic extracellular solution causes water to leave the cell, followed by cell shrinkage and damage to the intracellular matrix (especially protein) due to high-salt content. (NOTE: The extracellular osmolality of the prostatic tissue increases to approximately 8,000 mOsm by -15°C.) As the temperature approaches -15°C and below, lethal intracellular ice begins to form. In a structurally constrained organ (i.e., encapsulated), the expanding ice front may destroy cells of the capillary endothelial lining, rendering the vascular tree impaired after thawing.

The first principle of cryoablation is promotion of apoptosis. Apoptosis (genetically-regulated [programmed] cell death) has recently been linked with thermal injury.[36] Prostate cancer cells die from apoptosis following a freezing insult at temperatures consistent with the freeze-zone margin.[37] Apoptosis induction has been linked to a mitochondria-induced intrinsic mechanism characterized by an upregulation of cellular levels of Bax, the pro-apoptotic protein, without a concomitant change in pro-survival Bcl-2.[38] More recently, Clarke et al. have demonstrated that apoptotic induction can be facilitated in prostate cancer cells through an extrinsic pathway involving the interaction of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) with its receptor in the plasma membrane.[39]

The second principle of successful cryodestruction relates to procedural factors that maximize cancer cell kill (i.e., freeze rate, end-temperature, time, and freeze-thaw repetition). Contemporary cryosurgical technique provides precise "temperature management" of the targeted tissue with reliance on the combination of intraoperative ultrasound and temperature monitoring.[5,25,40] The destruction of both benign cells and cancer cells is dependent on an array

of physical freeze-related stresses. Prostate cell death follows a relatively precise temporal pattern. Cancer cells proximate to the CN/P or contained within the CN/P array are destroyed primarily by freeze rupture due to intracellular ice formation. The level of intracellular ice formation increases exponentially at temperatures less than -15°C. Throughout the frozen prostate, those cancers cells not destroyed by intracellular ice undergo either necrotic- or apoptotic-cell death depending on the extent of the stress experienced and the cell-cycle stage.[41]

Immediately post-thaw, some cancer cells will have experienced partial physical damage and will then undergo a bout of primary necrosis within one hour. This event, along with the presence of cell fragments resulting from freeze rupture, is responsible for the launch of the inflammation cascade. Simultaneously, and extending over approximately 6 to 12 hours, surviving cancer cells experience the onset of apoptosis stimulated by the biochemical stresses associated with the freeze concentration of inorganic and organic solutes. With progressive vascular stasis caused by freeze rupture of the tumor capillaries, local hypoxia results causing the induction (24 to 48 hours) of another bout of secondary necrosis.[42] These combined physical, structural, and biochemical insults render the prostate fully ablated.

In vitro and *in vivo* experiments demonstrate that human prostate cancer cells can be sensitized such that both apoptosis and secondary necrosis occur at greater rates when freezing is combined with cytotoxic agents.[43,44] This observation has been corroborated in other cancers.[45,46] Prostate cancer cells experiencing multiple molecular-targeted stressors (cytotoxic agents) succumb more readily to low-temperature exposure. In fact, very recent data indicate that with appropriate paired combinations, even freezing at -1°C can be totally lethal.[38,47,48] Neoadjuvant cryosurgery clinical trials will be needed to test these *in vitro* observations.

To both maximize the destructive effects of cryosurgery and to permit comparisons of outcomes among treatment centers, specific procedural requisites should be followed.[29]

- *Tissue Freeze Rate* – Rapid freezing is recognized as being more destructive than slow freezing. Cancer cells have the opportunity to "adapt" under conditions of slow freezing by losing water to the extracellular milieux, thereby reducing the probability of intracellular ice formation.

- *Temperature Monitoring* – The Panel strongly advises the use of thermocouples when performing cryosurgery despite the lack of supporting evidence-based documentation. The real-time measurement of tissue temperature at critical locations within and proximal to the prostate provides the urologist with an important indication of the status of the freezing process as well as protecting key vital structures such as the rectum and external urethral sphincter. Temperature monitoring is also facilitated by the ultrasound image. The advancing freeze zone is visualized as a hyperechoic rim (white line) on the ultrasound image. The distal edge of the hyperechoic rim represents the transition zone between frozen and unfrozen tissue. This transition occurs at -0.6°C. The inner edge of this rim (closest to CN/P) has been reported to be approximately -15°C to -20°C[34], the temperature of intracellular ice formation and maximum freeze concentration of solutes.

- *Nadir Temperature* – Throughout much of the history of cryosurgery, -40°C has been used as the end-temperature goal. Anecdotal evidence from both *in vivo* and *in vitro* studies as well as our knowledge of the physics of water all point to -40°C as being the lowest nominal temperature at which active human cells can survive.[34,37] It is recognized that prostate cancer is comparatively temperature labile with a lower lethal temperature near -20°C.[34,49]

- *Thaw Rate – In vitro* studies confirm that prostate cancer ablation is improved with slow (passive) thawing.[29] Activation of the heating mode in the CN/P does not affect the thaw rate of the distal edges of the gland. Probe heating affects only the frozen tissue mass juxtaposed to the CN/P and not the distally frozen tissue.

- *Freeze Cycles* – The Panel recommends the use of a double freeze-thaw cycle. Clinical experience, along with *in vivo* and *in vitro* studies, demonstrates that a clear benefit accrues with the use of a dual cycle.[29,50,51] Those cancer cells not killed by the first freezing are sufficiently stressed so that a second cycle is lethal. In addition, damage to tumor vascularity permits the second freeze to occur more rapidly and extends the -40°C isotherm further from the CN/P.

PART II

Primary Cryosurgery (Evidence Level II-2/3)

The consensus opinion of the Panel is that primary cryosurgery is an option, when treatment is appropriate, to men who have clinically organ-confined disease of any grade with a negative metastatic evaluation. High-risk patients may require multi-modal therapy. There are even more limited data regarding the outcomes for clinical T3 disease, and the role of cryosurgery in this setting is currently undetermined.

Patient Selection

Cryosurgery of the prostate is a locally ablative treatment option for the management of prostate cancer. Suitable candidates should have documented prostate cancer that is clinically confined to the prostate. Although cryosurgery is an option for low-, intermediate-, and high-risk

patients, gland volume is a factor; the larger the prostate, the more difficult to achieve a uniformly cold temperature throughout the gland. After assessment of volume and gland configuration, technical considerations will need to be made followed by appropriate technical modifications. In some larger glands, neoadjuvant cytoreduction can be considered to overcome the technical limitations of treating a large gland. Neoadjuvant or concomitant hormonal therapy, however, has not been shown to have a positive impact on subsequent cryosurgical outcomes.

The role of lymph node dissection in patients being considered for cryosurgery is similar to that in patients receiving radiation therapy. Elevated PSA levels (>20 ng/mL) or Gleason scores of 8 to 10 are associated with an increased incidence of lymph-node involvement. Men with a >25% risk based on established nomograms or some other published criteria may warrant lymph node dissection prior to or concurrent with cryosurgery (Appendix 4, Partin table[52]).[53] A prior history of transurethral resection of the prostate (TURP) is a relative contraindication for cryosurgery, especially if there is a large transurethral resection (TUR) defect present. These patients are at increased risk for urethral necrosis leading to sloughing and urinary retention due to failure of the urethral warming device to coapt to the mucosa. While many patients with elevated PSA levels have been treated with cryosurgery, the best results are achieved in patients with PSA levels <10 ng/mL.[54,55]

Cryosurgery is a minimally invasive option when treatment is appropriate for men who either do not want or are not good candidates for RP because of comorbidities, including obesity or a prior history of pelvic surgery. The latter is based on the opinion and experience of the Panel. Cryosurgery may also be a reasonable option in men with a narrow pelvis or who cannot tolerate external beam radiotherapy (EBRT), including those with previous nonprostatic pelvic radiation, inflammatory bowel disease, or rectal disorders. As cryosurgery is an outpatient

procedure or may only require an overnight stay, it is an option for patients seeking shorter-duration treatment of clinically organ-confined prostate cancer. For patients who desire minimally invasive therapy for their intermediate disease, defined as Gleason score 7 and/or Gleason score <8 with a PSA level >10 ng/mL but <20 ng/mL and/or clinical stage T2b, cryosurgery is also an option. [4,6,7,32]

Treatment Outcomes

Biochemical Outcomes

As with other therapies for prostate cancer, posttreatment PSA-level measurements are an integral part of follow-up. In the case of cryosurgery, however, there is no universally accepted biochemical definition of failure. PSA cut offs of <0.4 ng/mL, <0.5 ng/mL, <1.0 ng/mL, the old American Society for Therapeutic Radiology and Oncology (ASTRO) definition (three consecutive PSA rises) and, more recently, the new Phoenix biochemical definition of nadir plus 2 ng/mL, have been used, all of which may not be optimal surrogate endpoints following cryosurgery*. This dilemma of defining biochemical failure makes comparisons of the various treatments problematic especially when comparing total removal of the prostate to therapies that leave the prostate in situ. Because the urethra is preserved during cryosurgical ablation, there is always the potential that PSA-producing tissue will be preserved. For these reasons, a totally undetectable PSA level will not usually be attainable in the long term. It has been shown that the lower the PSA nadir, the greater the likelihood of a negative biopsy and a stable PSA over time.[11,56,57] A small number of publications have presented follow-up data ranging in duration from 5 to 10 years.[4-7,57] The five-year biochemical disease-free survival rates for low-, intermediate-, and high-risk cases range from 65% to 92%, 69% to 89%, and 48% to 89%,

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* In the PSA Best Practice Statement: 2009 Update the AUA defined biochemical recurrence as an initial PSA value less than or equal to 0.2 ng/mL followed by a subsequent confirmatory PSA value less than or equal to 0.2 ng/mL

respectively. More recently, a multicenter registry (the Cryoablation-On-Line-Database registry) of primary cryosurgery patients has reported pooled five-year biochemical outcomes. Using the old ASTRO definition, 85% of low-risk patients are disease free at five years, as are 73.4% of intermediate-risk patients and 75% of high-risk patients. This same cohort, when analyzed using the new Phoenix definition (nadir plus 2), shows similar results, with a 91% biochemical disease-free rate in the low-risk group at five years, 78% in the intermediate-risk group, and 62% in the high-risk group. The five-year biochemical disease-free survival rates reported since the year 2000 range as follows: 65% and 92% for low-risk disease[4,5], 69% and 89% for intermediate-risk disease, and 48% and 91% for high-risk disease. Long-term data regarding either metastasis-free or disease-specific survival for men undergoing cryosurgery are not currently available. As a consequence, meaningful comparisons of these reported outcomes from radical prostatectomy and radiation therapy to cryosurgery are not possible.

Posttreatment Biopsy Status

In many of the earlier published series describing the use of cryosurgery to treat prostate cancer, follow-up biopsy was a part of the treatment protocol. Biopsies were generally performed 6 to 12 months after treatment or for cause, such as rising PSA levels. The reported incidence of negative biopsy after one or more treatments is high, ranging from 87% to 98%.[4,5,12] Two of these studies biopsied virtually all participants, 73 of 76[5] and 590 of 590[4], while in the third report, 168 of 416 were biopsied.[12] In this latter report, the authors stopped their practice of performing routine posttreatment biopsies since the negative biopsy rate in the first 93 consecutive men exceeded 90%.[12] While a negative biopsy is not a guarantee of eradication of disease, a negative posttreatment biopsy potentially decreases the probability of treatment failure as reported following radiation therapy.[7,58]

Physician Reported Complications

Short term

Urinary retention usually persisting for one or two weeks postoperatively is treated with either a suprapubic or Foley catheter. After the freeze, the gland swells for a variable time, and the use of anti-inflammatory agents frequently helps. Penile and/or scrotal swelling are common in the first or second postprocedure weeks but are self-limiting, usually resolving within two months. Penile paresthesia may occur, especially if the anterior probes are maximally driven. This side effect usually resolves within two to four months.

Long term

Fistula formation. In the 1960s and 1970s, with the earlier forms of cryosurgery technology, fistula formation was the most significant complication and continued to be a concern in the early 1990s when cryosurgery was reintroduced. The patients at highest risk were those treated with salvage cryosurgery after radiation therapy. This is not a common complication in primary treated patients and, in the last 10 years, the incidence of this complication has become uncommon. The incidence reported in the literature ranges between 0% to 0.5%.[4-6,10] Thus, the risk of fistula formation is the same as the risk of rectal injury following RP, various forms of EBRT, and interstitial prostate brachytherapy.

Incontinence. In complete gland cryosurgery, the external sphincter is inevitably affected by the freeze, although it is somewhat protected by the urethral-warming catheter, as is the prostatic urethral mucosa. Nonetheless, there is a risk of urinary incontinence, and when present, is usually limited to mild stress incontinence. The incidence of permanent physician reported incontinence (wearing a pad) in the literature ranges from <1% to 8%.[12]

Erectile Dysfunction. During total gland cryosurgery, the ice ball extends outside the prostate

capsule and in most cases encompasses both neurovascular bundles, commonly resulting in erectile dysfunction. The incidence of erectile dysfunction reported in the literature ranges from 49%[4,5] to 93% at one year. For this reason, cryosurgery is generally considered suitable as a treatment option in men who are not concerned with erectile function. A recent study of penile rehabilitation following total gland cryoablation reports a potency rate of 41.4% at one year and 51.3 % at four years.[12]

Urethral sloughing. The use of a urethral-warming catheter, currently a standard technique of the operative procedure during the freeze, has been shown to significantly reduce the risk of urethral sloughing.[50,59] On occasion, however, its protective effect can be overcome. Urethral sloughing is particularly likely to occur in the sulcus on either side of the verumontanum, which is frequently not in contact with the urethral-warming catheter surface. As a result, the prostatic mucosa can necrose, forming a linear ulcer, exposing the necrotic prostate tissue to urine flow. Severe dysuria and urinary retention can result and may require TUR of the necrotic tissue to overcome the problem, the outcomes of which have not been reported. The currently reported incidence of urethral sloughing in patients undergoing cryosurgery with the use of a urethral-warming catheter ranges from 0% to 15%.[57,59]

Mouraviev and Polascik[60] recently summarized in tabular form the more common complications associated with primary cryosurgery of the prostate (Table 1).[6,13,23,54,56,60-63] It is thought that the high morbidity presented in earlier series could be attributed to the use of liquid nitrogen-based systems, older ultrasound techniques, and banning of the urethral warmer by the United States (US) Food and Drug Administration (FDA).[60] Cohen, using a large single-institution database, compared the complications of cryosurgery with the use of nitrogen- and

argon-based equipment and showed that this technological change has led to a decrease in serious side effects such as incontinence and fistulas.[13]

Table 1. Complication rates after Primary cryosurgery of the prostate

Reference	Year	No. pts.	Cryosystem	Erectile Dysfunction (%)	Incontinence (%)	Fistula (%)	Urethral stricture (%)	Urethral sloughing (%)	Perineal Pain (%)	Obstruction/ retention (%)	UTI/sepsis (%)
Primary Cryosurgery											
Bahn et al.[63]	1995	210	Cryocare	41	9	2.4	NA	NA	NA	3	NA
Shinohara et al.[56]	1997	102	NA	86	15	1	NA	23	3	23	3/3
Cohen et al.[23]	1995	239	Cryocare Seednet	4	0.4	2.2	NA	9.8	0.4	3	2.2/0.7
Wake et al.[61]	1996	100	Cryocare	NA	8	0	NA	1	NA	22	NA
Long[54]	1996	145	Cryocare	88	2	1.3	3.4	8.9	2.3	17	2.3/<1
Badalament et al.[62]	1999	290	Cryocare	85	4.3	0.4	NA	10	12	NA	NA
Long et al.[6]	2001	975	Cryocare	NA	7.5	0.5	NA	NA	NA	13	NA
Cohen[13]	2004	865	Accuprobe (before 1996)	NA	8.6	2	NA	16	NA	NA	NA
			Cryocare (1996-2000)	NA	3.2	0	NA	14	NA	NA	NA
		98	Seednet	NA	0	0	NA	2	NA	NA	NA

No. pts. – number of patients; NA – not available; UTI – urinary tract infection.

Adapted from Mouraviev and Polascik, reprinted in part with permission.[60]

Health-related Quality of Life

In a prospective, longitudinal comparative study of early (six months), Health-related Quality of Life (HRQL) outcomes in patients undergoing one of five surgical approaches (including open, laparoscopic, and robotic prostatectomy as well as cryosurgery and brachytherapy {Palladium Pd}) from a single institution, Ball et al. concluded that each of the different surgical approaches affected HRQL results in different ways.[3] Cryosurgery had a higher negative impact compared to interstitial therapy for both sexual and urinary function at three months. Cryosurgery's impact on urinary function was equivalent to that of brachytherapy by six months and cryosurgery had superior AUA symptom scores at three months for irritative and obstructive symptoms. Published initially in 1999[64] and updated in 2002[8], Robinson et al. reported 36-month data from 64 of 75 patients who had completed the Functional Assessment of Cancer Treatment-Prostate (FACT-P) questionnaire as part of a Phase II trial of cryosurgery as primary therapy for localized prostate cancer. Despite a decrease in scores from baseline to six weeks after surgery, by 12 months there were no significant differences compared with baseline scores with the exception of sexuality. Satisfaction in this area decreased significantly over the first six weeks and slowly improved over the next two years. Nevertheless, scores in this domain remained below baseline levels. No significant changes were noted in any category between year one as presented in the first publication and year three in the second publication, suggesting that HRQL remains stable after the first year and that there were no reported delayed complications following the first year of cryosurgery.

PART III

Salvage Cryosurgery (Evidence Level II-3)

It is the opinion of the expert Panel that salvage cryosurgery can be considered as a treatment option for curative intent in men who have failed radiation therapy. The most appropriate candidates have biopsy proven persistent organ-confined prostate cancer, a PSA <10 ng/mL, and a negative metastatic evaluation as determined by standard assessment tools such as imaging modalities.[51]

Introduction

Radiation is a common form of therapy for patients with newly diagnosed and localized prostate cancer. It has been estimated that nearly one-third of newly diagnosed prostate cancer patients will choose one form of radiation therapy as their primary treatment. Despite modifications of delivering radiation such as intensity modulation, 3-dimensional conformal, and computer-assisted brachytherapy, a number of these patients will have a rise in their serum PSA value sometime after radiation. Since rising PSA levels can occur with both local and metastatic disease, an elevation does not necessarily imply that a patient has local recurrence. In addition, a minimal PSA level elevation may be due to benign causes. These factors make it difficult to clearly define a locally salvageable population. After radiation therapy, a prostate biopsy will be positive in one-third of patients with biochemical failure.[65] If local recurrence is detected early and occurs without clinical evidence of metastatic disease, salvage therapy is feasible. Recent advances in both technology and the technique of salvage cryosurgery have reduced treatment-associated morbidity and stimulated interest in this treatment option for curative intent in the setting of radiation failure.[29,51,55,66-68]

Patient Selection

PSA Levels

The optimal time for intervention in a patient whose postradiation treatment PSA increases is unclear. A temporary rise in PSA levels after brachytherapy commonly occurs around 20 months after treatment.[69] This "bounce phenomenon" has also been described in patients following EBRT.[70] Although there is no consensus among urologists or radiation oncologists regarding the timing of salvage therapy, the clinician should consider variables such as stage of disease at presentation, existing comorbidities, patient age, and patient preference. If the PSA level rises acutely and persists above the nadir level or the patient is deemed to have failed clinically based on any currently employed evaluation tool (ASTRO, Phoenix, PSA doubling time/velocity), a prostate biopsy should be performed if there are no contraindications to further therapeutic intervention. The Partin table[52] for predicting pathologic stage does not apply to postradiation therapy patients. The patient with a PSA of 10 ng/mL following radiation should not be considered to have the same pathology as a nonradiated patient with a PSA of 10 ng/mL. According to Spiess et al., a PSA level >10 ng/mL at the time of diagnosis of local recurrence and a PSA doubling time ≤16 months will predict a poor response to salvage cryosurgery.[71] If PSA doubling time is ≤6 months, there is a significantly higher risk of metastasis in addition to local disease.[72]

Prostate Biopsy

It is the consensus of this panel that a prostate biopsy should be performed when considering salvage cryosurgery and that only men with a positive result should undergo cryosurgery. When a biopsy is undertaken, multiple cores should be obtained, and the pathologists should be informed that the patient has had previous radiation since there are

definite pathological changes that can occur postradiation. Benign glands affected by radiation can mimic cancerous glands, and special staining with high molecular weight keratin and other molecular markers may be necessary to make a correct diagnosis.[73] A positive biopsy prior to 36 months after radiation treatment can be extremely difficult to interpret since malignant glands may slowly undergo apoptosis. Consequently, an experienced interpretation of the postradiation biopsy specimen is essential. As with biopsies in the nonradiated patient, there are no definite guidelines specifying the number of cores that should be obtained. Recent literature has indicated that extended biopsy strategies, albeit not in the posttreatment setting, enhance the detection of cancer and that sextant biopsies are no longer considered adequate. Although there is an absence of supporting documentation, biopsy of both seminal vesicles (SVs) is recommended by this panel in addition to a prostate biopsy. Cancer-invaded SVs may appear normal on imaging after radiation therapy. The incidence of SV involvement in a patient status postradiation therapy with a rising PSA is higher than in a nonradiated patient with a similar PSA history. Pathological results from salvage RP series reveal that the rate of SV involvement can be as high as 42%.[74] Those patients with SV invasion have a poor prognosis, despite successful local treatment of the prostate gland. In the presence of SV involvement, prostate salvage cryosurgery as monotherapy is not likely to be successful.[75]

Metastatic Work-up

If a prostate biopsy reveals recurrent cancer in the gland, a metastatic evaluation including lymph node assessment with imaging of the abdomen and pelvis as well as a bone scan should be performed. Open or laparoscopic biopsy of the pelvic lymph nodes

may also be considered for high-risk patients. The lymph node positivity rate in patients from the salvage radical prostatectomy series ranges between 5% and 30%.[75-78]

Other Factors

Prostate size is less of a problem when considering salvage cryosurgery since the prostate of radiated patients loses volume after radiation therapy. A prior history of transurethral resection of the prostate is a relative contraindication for salvage cryosurgery, especially if there is a large TUR defect present, as these patients are at risk for urethral necrosis leading to sloughing and urinary retention.

Patient Selection Summary

Currently, there are no clearly defined guidelines to aid in the proper selection of patients for salvage cryosurgery. The optimal candidates for the procedure are men who have pathologic evidence of locally recurrent disease without clinical evidence of metastatic disease, a PSA $\leq$4 ng/mL[79], a long PSA doubling time[71,80], no evidence of SV invasion, and a life expectancy >10 years.[81]

Technical Considerations and Modifications

Salvage cryosurgery can be performed in the patient with recurrent disease following EBRT as well as interstitial prostate brachytherapy. Previously placed radioactive seeds can be visualized quite well under TRUS and may cause some confusion as their sonographic appearance is similar to the tip of the cryoneedles, especially in the transverse view. Placing the needles in the sagittal plane can overcome this difficulty, since the length of the cryoneedles can be easily followed in this view. Due to previous radiation, the gland may be adherent to the anterior rectal wall, diminishing the thickness of Denonvilliers' fascia. This needs to be assessed by TRUS

prior to freezing so the surgeon can determine how to appropriately place the posterior cryoprobes and the Denonvilliers' thermocouple. If the space between the anterior rectal wall and posterior prostatic capsule is <5 mm, it may not be possible to drive the temperatures down to –40°C safely, and freezing should be terminated when the leading edge of the ice ball has extended just beyond the capsule, even if the target temperature of –40°C is not reached. Double freeze-thaw cycles have better outcomes in terms of biochemical failure-free and local recurrence-free survival rates compared to a single freeze-thaw cycle.[51]

When counseling patients for any salvage procedure, the risks of urinary incontinence need to be addressed. Placement of a thermosensor to monitor the temperature of the external sphincter can reduce the potential of thermal injury to this muscle. The thermosensor is introduced through the perineal skin and advanced until the impression of the tip of the thermocouple can be seen in the sphincter. The placement can be documented by TRUS with/without cystoscopy.

There is no documented evidence of benefit from hormone therapy prior to salvage cryosurgery except for downsizing purposes.

Treatment Outcomes

Biochemical Outcomes

Over the past decade, several institutions have published their salvage cryosurgery results. Many of the published series from the mid 1990s had significant numbers of complications.[51,82] Despite the inability to adequately control the ice formation and target the gland in this "early" cryosurgery period, follow-up PSA values and biopsy data with their known limitations indicate that the introduction of lethal ice

could eradicate radio-resistant, locally-aggressive cancer. The high morbidity presented in these reports could be attributable to a number of factors. For one, the use of thermocouples was not yet available. In addition, there was a period of time when the United States Food and Drug Administration ordered a recall of the urethral-warming device and, as a consequence of inadequate warming, urethral sloughing was prevalent, resulting in pain, urinary retention, and incontinence. Furthermore, early studies were performed using a liquid nitrogen-based system that limited the ability to control the growth of the ice ball. This, coupled with improper cryoprobe placement, led to the development of rectal fistulas.

The introduction of argon-based cryosurgical equipment led to significant advances in the technology. The use of pressurized argon gas, multiple probes, and use of thermosensors have produced better results compared to liquid nitrogen-based systems for locally recurrent cancer.[51,57,68] Although there has been no established set of parameters to define success or failure after salvage cryosurgery, persistent disease diagnosed by prostate biopsy and a stable PSA value up to 0.5 ng/mL are commonly used to define outcomes.

Using two freeze-thaw cycles, Cespedes et al. achieved a biopsy-negative rate of 93% and a biochemical failure-free survival rate of 66% in a series of 150 patients treated by the liquid nitrogen-based system.[83] These results, however, came at the price of high-complication rates.[83] Patients with preoperative PSA levels >10 ng/mL or Gleason scores ≥8 were most likely to experience disease recurrence.[51] Bahn et al. reported seven-year salvage biochemical failure-free rates of 59% and 69% using cut-off values of PSA <0.5 ng/mL and <1.0 ng/mL, respectively, in 59 patients.[55]

de la Taille et al. reported a biochemical failure-free survival rate of 66% at 12 months in a series of 43 salvage patients, with low-complication rates.[84] In their experience, a PSA nadir of >0.1 ng/mL following treatment predicted eventual recurrence.[85] Ghafar et al. used an argon-based cryosurgery system to treat 38 patients with biochemical recurrence after radiation.[28] Cresswell et al. reported 67% biochemical failure-free rate as defined by PSA levels <0.5 ng/mL for 20 salvage cryosurgery patients.[86] Han et al. also reported a 74% biochemical failure-free rate at one year with an argon-based system.[32] Ghafar et al. reported PSA nadirs <0.1 ng/mL in 81.5%, and biochemical disease-free rates of 86% and 74% at one and two years, respectively.[28] In another recently published large series also employing an argon-based system, Chin et al. performed cryosurgery on 118 patients with recurrent disease after radiation therapy, including five who had received permanent interstitial implants.[66] They reported negative biopsies in 94% of these patients; the seven who had persistent disease underwent a second ablation procedure. In this series, 97% of patients had PSA nadirs <0.5 ng/mL, 34% remain below this level with a median follow-up of 18.6 months (68% had PSA <4 ng/mL, and 10 patients developed metastatic disease). As in the Pisters et al. study[51], preprocedure PSA levels >10 ng/mL, Gleason score ≥8, and stage T3/4 disease predicted biochemical failure.[66]

Physician Reported Complications

Recent advances in technology have reduced the complication rates associated with salvage cryosurgery (Table 2[28,51,60,66,87,88]). In the past, incontinence rates following salvage cryosurgery exceeded 70%[51], but current studies report rates <10%.[28,32,66,84] Despite these improvements, incontinence rates in the salvage setting are still higher

compared to those following primary cryosurgery. A recent study reported an

improvement in the incontinence rate following salvage cryosurgery by leaving the

urethral warmer in place for 60 to 90 minutes.[88] Rectourethral fistula was also reported

to occur more frequently in salvage cases; however, recent studies report this serious

complication has been significantly diminished (0% to 3%).[28,32,84] Although rectal fistula

is currently rare, rectal pain has been reported. In a series of 35 patients who underwent

cryosurgery of the prostate with an argon-based system, 37% who had prior radiation

therapy had pain compared with 12% of patients who underwent primary cryosurgery.[85]

In a later study, Donnelly et al. reported that rectal pain occurred in 17% (8 of 46) of

salvage patients.[67] The cause of the pain is unknown but may be related to an ischemic

event that occurs near the anterior rectal wall. After radiation, there may be reduced

blood supply to this area and introducing lethal ice may elicit further devascularization.

Urethral sloughing and obstruction can be seen in 5% to 10% of patients.[28,32,84] Even with

the current technologies and techniques, erectile dysfunction rates remain high at >80%.

Table 2. Complication rates after Salvage cryosurgery of the prostate

Reference	Year	No. pts.	Cryosystem	Erectile Dysfunction (%)	Incontinence (%)	Fistula (%)	Urethral stricture (%)	Urethral sloughing (%)	Perineal Pain (%)	Obstruction/ retention (%)	UTI/sepsis (%)
Salvage Cryosurgery											
Pisters et al.[51]	1997	150	Accuprobe	72	73	1	NA	NA	NA	67	NA
Chin et al.[66]	2001	118	Cryocare	NA	6.7	3.3	0	5	NA	8.5	0
Ghafar et al.[28]	2001	38	Seednet	NA	7.9	0	0	0	NA	4	0
Han and Bellegrun[87]	2004	29	Seednet NA	NA	9	0	0	0	NA	3	0
Katz et al.[88]	2005	157	Cryocare Seednet	NA	9.7	0	0	0	12.8	5.8/1.9	0

No. pts. – number of patients; NA – not available; UTI – urinary tract infection.

Adapted from Mouraviev and Polascik, reprinted in part with permission.[60]

Health-related Quality of Life

There are two series reporting HRQL data in patients undergoing salvage cryosurgery with argon-based devices. Robinson et al. assessed HRQL using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 instrument and the Prostate Cancer Index in 46 patients at baseline and 24 months following salvage cryosurgery.[89] HRQL returned to preoperative levels by 24 months in all domains, with the exception of urinary and sexual functioning. At 24 months, 29% of patients reported urinary bother as a moderate to big problem, and 56% reported sexual bother as a moderate to big problem. Thus, impairments in long-term HRQL following argon-based salvage cryosurgery seem to be limited to the sexual and urinary function domains.[89] Anastasiadis et al. compared HRQL in 51 primary cryosurgery patients compared to 31 salvage cryosurgery patients using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire -C30 instrument.[90] The overall HRQL scores were high in both groups. Primary cryosurgery patients reported higher physical (p=0.005) and social (p=0.024) functioning compared with salvage patients.[90] Sexual function, urinary symptoms, and incontinence were more common in the salvage patients. These results are not surprising and are analogous to the higher-complication rates reported in patients undergoing postradiation salvage RP compared to primary RP.[75,78,91,92] It is important to note that there are no reports comparing HRQL before and after other salvage local therapies such as salvage RP or salvage brachytherapy. Thus, it is not possible to directly compare HRQL outcomes among the various salvage local treatments.

Summary

Cryosurgery guided by ultrasound and temperature monitoring is an option for recurrent clinically organ-confined prostate cancer after radiation therapy. As with other salvage therapies for curative intent, cryosurgery should be considered early for patients defined as radiation failures. Refinements in the surgical technique and equipment have resulted in significantly less morbidity than previously reported as well as encouraging short-term PSA results. Economic modeling is needed to assess the cost effectiveness of salvage cryosurgery relative to alternative treatments.

PART IV

Subtotal Prostate Cryosurgery (Evidence Level III)

While this minimally invasive technique of cryosurgery is attractive from a conceptual perspective, clinical experience is limited[93] and long-term results are unavailable. The Panel's consensus is that cases of subtotal prostate cryoablation should be collected prospectively in a database for future analysis.

The criteria for patient selection for subtotal prostate cryosurgery have yet to be determined. This procedure may fill a void in the therapeutic options available to men who are potential candidates for active surveillance who prefer therapy or for men with clinically organ-confined unilateral significant disease (yet to be defined). Theoretically, this targeted approach has the potential to customize treatment and address the growing concerns of both over and undertreatment. However, current data are insufficient to determine the incidence or consequences of treatment failure.

Overview Conclusions

While there is no Level I evidence from prospective, randomized trials to support the role of cryosurgery over other therapeutic options in the treatment of prostate cancer, the literature contains documentation reporting the seven- to eight-year biochemical disease-free results of cryosurgery. The literature reports that the morbidity profile associated with cryosurgery has improved in all aspects, including continence, rectal/urethral fistula formation, urethral sloughing, and potency[12] in association with the technological advances over the last 10 to 15 years.

Conflict of Interest Disclosures

All panel members completed Conflict of Interest disclosures. Those marked with (C) indicate that compensation was received; relationships indicated by (U) indicate no compensation was received.

Consultant or Advisor: Richard J. Babaian, Endocare (C); Aaron Katz, Oncura (C), Endocare (C); Louis Pisters, Endocare (C); Martin Dineen, Abbeymoor Medical Inc. (C), Endocare (C); Bryan Donnelly, Endocare (C); Katsuto Shinohara, Nihon Mediphysics (C), Wilex AG (C); **Investigator:** Louis Pisters, Protox Therapeutics (C); **Scientific Study or Trial:** Martin Dineen, Oakwood Pharmaceuticals (C), Duramed (C), Amgen (C), National Cancer Institute – Johns Hopkins (C), Mentor (C), Sanofi (C), GlaxoSmith-Kline (C), AstraZeneca (C), Schering Plough (C), GTX (C); Katsuto Shinohara, KineMed (C), GlaxoSmithKlein (U); **Meeting Participant or Lecturer:** John G. Baust, Galil Medical (C); **Other:** Richard J. Babaian, Gen-Probe (C); David Ellis, Endocare (C).

Acknowledgements and Disclaimers

AUA Best Practice Statement on Cryosurgery for the Treatment of Localized Prostate Cancer

The supporting systematic literature review and the drafting of this document were conducted by the Cryosurgery for Treatment of Localized Prostate Cancer Best Practice Statement Panel (the Panel) created in 2005 by the American Urological Association Education and Research, Inc. (AUA). The Practice Guidelines Committee (PGC) of the AUA selected the Panel chair and facilitator who in turn appointed the additional Panel members with specific expertise in this disease.

The mission of the Panel was to develop either analysis- or consensus-based recommendations, depending on the type of evidence available and Panel processes, to support optimal clinical practices in the cryosurgical treatment of localized prostate cancer. This document was submitted to approximately 64 urologists and other health care professionals for peer review. After revision of the document based upon the peer review comments, the best practice statement was submitted to and approved by the PGC and the Board of Directors of the AUA. Funding of the Panel and of the PGC was provided by the AUA, although Panel members received no remuneration for their work. Each member of the PGC and of the Panel furnished a current conflict of interest disclosure to the AUA.

The final report is intended to provide medical practitioners with a current understanding of the principles and strategies for the cryosurgical treatment of localized prostate cancer. The report is based on review of available professional literature, as well as clinical experience and expert opinion.

This document provides guidance only and does not establish a fixed set of rules or define the legal standard of care. As medical knowledge expands and technology advances, this best practice statement will change. Today they represent not absolute mandates but provisional proposals or recommendations for treatment under the specific conditions described. For all these reasons, this best practice statement does not preempt physician judgment in individual cases. Also, treating physicians must take into account

variations in resources and in patient tolerances, needs, and preferences. Conformance with the best practice statement reflected in this document cannot guarantee a successful outcome.

Appendix 1. Cryosurgery for the Treatment of Localized Prostate Cancer Best Practice Statement Panel

Richard J. Babaian, M.D.
Urology Department
MD Anderson Hospital
Houston, Texas

Duke Bahn, M.D.
Ventura, California

John G. Baust, Ph.D.
Institute of Biomedical Technology
Binghamton University
State University of New York
Binghamton, New York

Martin Dineen, M.D.
Atlantic Urology
Daytona Beach, Florida

Bryan Donnelly, M.D.
University of Calgary
Calgary, Alberta, Canada

David Ellis, M.D.
Urology Associates of North Texas
Arlington, Texas

Aaron Katz, M.D.
Herbert Irving Cancer Center
New York, New York

Louis L. Pisters, M.D.
Professor of Urology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Daniel Rukstalis, M.D.
Geisinger Medical Center
Danville, Pennsylvania

J. Brantley Thrasher, M.D.
University of Kansas
Department of Urology
Kansas City, Kansas

Katsuto Shinohara, M.D.
University of California, San Francisco
San Francisco, California

John Forrest, M.D.
PGC Representative to the Panel
Urologic Specialist of Oklahoma
Tulsa, Oklahoma

Appendix 2. Levels of Evidence

In this best practice statement, the treatment recommendations were rated according to

the levels of evidence published from the U.S. Preventive Services Task Force:[15]

- I   Evidence obtained from at least one properly randomized controlled trial.

- II–1   Evidence obtained from well-designed controlled trials without randomization.

- II–2   Evidence obtained from well-designed cohort or case control analytic studies, preferably from more than one center or research group.

- II–3   Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

- III   Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

Appendix 3. Definitions

For the purposes of this document, the panel considered first generation procedures to be those employing liquid nitrogen-based systems. Argon-based systems comprise the second and third generation procedures.

Appendix 4. Partin Table

TABLE I. *Clinical Stage T1c (nonpalpable, PSA elevated)*

PSA Range (ng/mL)	Pathologic Stage	Gleason Score 2–4	5–6	3 + 4 = 7	4 + 3 = 7	8–10
0–2.5	Organ confined	95 (89–99)	90 (88–93)	79 (74–85)	71 (62–79)	66 (54–76)
	Extraprostatic extension	5 (1–11)	9 (7–12)	17 (13–23)	25 (18–34)	28 (20–38)
	Seminal vesicle (+)	—	0 (0–1)	2 (1–5)	2 (1–5)	4 (1–10)
	Lymph node (+)	—	—	1 (0–2)	1 (0–4)	1 (0–4)
2.6–4.0	Organ confined	92 (82–98)	84 (81–86)	68 (62–74)	58 (48–67)	52 (41–63)
	Extraprostatic extension	8 (2–18)	15 (13–18)	27 (22–33)	37 (29–46)	40 (31–50)
	Seminal vesicle (+)	—	1 (0–1)	4 (2–7)	4 (1–7)	6 (3–12)
	Lymph node (+)	—	—	1 (0–2)	1 (0–3)	1 (0–4)
4.1–6.0	Organ confined	90 (78–98)	80 (78–83)	63 (58–68)	52 (43–60)	46 (36–56)
	Extraprostatic extension	10 (2–22)	19 (16–21)	32 (27–36)	42 (35–50)	45 (36–54)
	Seminal vesicle (+)	—	1 (0–1)	3 (2–5)	3 (1–6)	5 (3–9)
	Lymph node (+)	—	0 (0–1)	2 (1–3)	3 (1–5)	3 (1–6)
6.1–10.0	Organ confined	87 (73–97)	75 (72–77)	54 (49–59)	43 (35–51)	37 (28–46)
	Extraprostatic extension	13 (3–27)	23 (21–25)	36 (32–40)	47 (40–54)	48 (39–57)
	Seminal vesicle (+)	—	2 (2–3)	8 (6–11)	8 (4–12)	13 (8–19)
	Lymph node (+)	—	0 (0–1)	2 (1–3)	2 (1–4)	3 (1–5)
>10.0	Organ confined	80 (61–95)	62 (58–64)	37 (32–42)	27 (21–34)	22 (16–30)
	Extraprostatic extension	20 (5–39)	33 (30–36)	43 (38–48)	51 (44–59)	50 (42–59)
	Seminal vesicle (+)	—	4 (3–5)	12 (9–17)	11 (6–17)	17 (10–25)
	Lymph node (+)	—	2 (1–3)	8 (5–11)	10 (5–17)	11 (5–18)

Key: PSA = prostate-specific antigen.

TABLE II. *Clinical Stage T2a (palpable <½ of one lobe)*

PSA Range (ng/mL)	Pathologic Stage	Gleason Score 2–4	5–6	3 + 4 = 7	4 + 3 = 7	8–10
0–2.5	Organ confined	91 (79–98)	81 (77–85)	64 (56–71)	53 (43–63)	47 (35–59)
	Extraprostatic extension	9 (2–21)	17 (13–21)	29 (23–36)	40 (30–49)	42 (32–53)
	Seminal vesicle (+)	—	1 (0–2)	5 (1–9)	4 (1–9)	7 (2–16)
	Lymph node (+)	—	0 (0–1)	2 (0–5)	3 (0–8)	3 (0–9)
2.6–4.0	Organ confined	85 (69–96)	71 (66–75)	50 (43–57)	39 (30–48)	33 (24–44)
	Extraprostatic extension	15 (4–31)	27 (23–31)	41 (35–48)	52 (43–61)	53 (44–63)
	Seminal vesicle (+)	—	2 (1–3)	7 (3–12)	6 (2–12)	10 (4–18)
	Lymph node (+)	—	0 (0–1)	2 (0–4)	2 (0–6)	3 (0–8)
4.1–6.0	Organ confined	81 (63–95)	66 (62–70)	44 (39–50)	33 (25–41)	28 (20–37)
	Extraprostatic extension	19 (5–37)	32 (28–36)	46 (40–52)	56 (48–64)	58 (49–66)
	Seminal vesicle (+)	—	1 (1–2)	5 (3–8)	5 (2–8)	8 (4–13)
	Lymph node (+)	—	1 (0–2)	4 (2–7)	6 (3–11)	6 (2–12)
6.1–10.0	Organ confined	76 (56–94)	58 (54–61)	35 (30–40)	25 (19–32)	21 (15–28)
	Extraprostatic extension	24 (6–44)	37 (34–41)	49 (43–54)	58 (51–66)	57 (48–65)
	Seminal vesicle (+)	—	4 (3–5)	13 (9–18)	11 (6–17)	17 (11–26)
	Lymph node (+)	—	1 (0–2)	3 (2–6)	5 (2–8)	5 (2–10)
>10.0	Organ confined	65 (43–89)	42 (38–46)	20 (17–24)	14 (10–18)	11 (7–15)
	Extraprostatic extension	35 (11–57)	47 (43–52)	49 (43–55)	55 (46–64)	52 (41–62)
	Seminal vesicle (+)	—	6 (4–8)	16 (11–22)	13 (7–20)	19 (12–29)
	Lymph node (+)	—	4 (3–7)	14 (9–21)	18 (10–27)	17 (9–29)

Key: PSA = prostate-specific antigen.

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