
A Critical Review of Clinical Practice Guidelines for the Management of Clinically Localized Prostate Cancer

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Purpose: Increasingly there is a recognized need for the development of high quality, evidenced-based clinical guidelines to assist clinicians and patients in critically important treatment related decision making. We review the different approaches used by leading urological organizations to develop guidelines for the management of clinically localized prostate cancer and their specific recommendations for case management.

Materials and Methods: Guidelines for the management of localized prostate cancer developed by leading professional organizations were identified through the National Guidelines ClearinghouseTM, PubMed[®], cited references and personal communication with prostate cancer experts. A structured data abstraction was applied to assess how the guideline was developed, what type of professionals and stakeholders were involved in the development process, how the primary evidence was identified and graded, and what specific final recommendations were reported.

Results: Clinical practice guidelines on the management of clinically localized prostate cancer demonstrate major differences in their specific recommendations. Few recommendations are based on high level evidence, and there are considerable discrepancies among the systems used to grade the quality of the evidence and the strength of the recommendations.

Conclusions: There appears to be a need to standardize the process used by leading urological organizations to develop clinical guidelines for the management of prostate cancer. A unified approach may offer considerable rewards in terms of efficiency, guideline credibility and optimal clinical decision making. Furthermore, increased efforts are indicated to promote studies that yield high quality evidence to guide the management of prostate cancer.

Key Words: practice guideline (publication type), prostatic neoplasms, evidence-based medicine

Leading organizations increasingly recognize clinical practice guidelines as an important approach to promoting evidence-based practice in urology. These guidelines have been defined as “systematically developed statements to help practitioner and patient decisions about appropriate health care for specific clinical circumstances.”¹ Guidelines differ from systematic reviews, cost analyses and decision models in that they make explicit recommendations aimed at influencing clinician behavior. As such, they provide recommendations for typical patients that have been systematically developed by panels of individuals with access to the available evidence, an understanding of the clinical problems and research methods, and sufficient time for consideration.

However, for specific recommendations to find their way into clinical practice, potential users must be convinced that the methods and processes by which they were developed were valid, and not unduly biased by a special interest party. An explicit and ideally unified system for grading the quality

of evidence and recommendations would be a major contribution to the more widespread acceptance of such guidelines.^{2,3} A unified approach would also help mitigate the confusion among users of guidelines about how guidelines are developed. In light of the considerable clinical, economic and medicolegal impact that guidelines can have, users should be convinced that they were rigorously developed and address patient relevant issues. We critically review the methods used by leading organizations to develop guidelines for managing localized prostate cancer as well as their specific recommendations. In addition, we introduce methodology that was developed by the GRADE working group as an example of how these issues can be addressed and as a potential unified approach to guideline development for all organizations.^{4,5}

MATERIALS AND METHODS

Clinical practice guidelines for the management of localized prostate cancer by leading professional organizations were identified through the National Guidelines Clearinghouse, PubMed and cited references, which were further supple-

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mented by information from prostate cancer experts. The search terms used were “prostate cancer” and “prostatic neoplasms.” In PubMed these terms were combined with the search terms “practice guidelines,” “recommendations” and “consensus development conference,” using appropriate Boolean operators. The search was limited to prostate cancer guidelines that were published during the last 10 years (1997 to 2007). Only clinical practice guidelines that included clinically localized prostate cancer within their scope and that were not limited to a single treatment modality (ie external beam radiation therapy) were included in the review. Furthermore, only guidelines published by professional societies, and national and international government agencies were considered. Local and single institution guidelines were excluded. One guideline document was excluded because it was not developed separately but represented an adaptation of guidelines by a different organization.⁶

A structured data abstraction was applied that was developed from instruments published in the guidelines methodology literature.⁷⁻⁹ We assessed how the guidelines were developed, what type of professionals and stakeholders were involved in the development process, how the primary evidence was identified and graded, and what specific recommendations were made. Data abstraction was performed by 2 independent reviewers (PD and LLY). Discrepancies were settled by discussion and consensus. All assessments were based on the published full text versions of the guidelines as well as supporting documentation as referenced.

PROSTATE CANCER GUIDELINES

Clinical practice guidelines by 7 leading professional organizations that address the management of localized prostate cancer were identified and critically reviewed.

AUA Guidelines

The original AUA guidelines for clinically localized prostate cancer were published in 1995 and were developed during a 6-year period by 17 clinicians and scientists.¹⁰ Development required the evaluation of 12,501 scientific publications and the detailed extraction of 165 articles that met the criteria established by the panel. For more than a decade this document served as the official AUA guidelines for its members and was not updated until recently, thereby reflecting one of the major challenges faced by guidelines developers, which is timeliness.¹¹ Efforts to revise the AUA prostate cancer guidelines began in 2001 and took more than 5 years to complete. The main recommendations were first presented at the AUA annual meeting in 2006, followed by the full text publication in *The Journal of Urology*[®] and on the AUA website (www.auanet.org/guidelines) in 2007.

The key methodological characteristics of the AUA prostate cancer guidelines development process are presented in Appendix 1. The AUA guidelines clearly describe the individuals involved in the guidelines development as a panel of 16 members from all key disciplines as well as a team of 5 external consultants with specific expertise in systematic literature searches, data abstraction and clinical pharmacology. The National Library of Medicine was used as the single data source and was searched using PubMed. English language references that were published in full text from 1991 to early 2004 were included based on 3 separate individual searches. Of 13,888 citations only 436 met the pre-

defined inclusion criteria and were included in the data analysis. A majority of the studies (352 of 436 or 81%) were retrospective case series and only 6% were controlled clinical trials.

The process of data abstraction was clearly outlined and included several quality checks to ensure accuracy. The data were then compiled and presented to the guidelines panel for discussion. No level of evidence grading system was applied to studies considered by the guidelines panel and no formal process as to how the recommendations were formulated was reported. Although they were not pilot tested, the AUA guidelines were peer reviewed by 87 urologists and other health care professionals. The guidelines document addresses how the guidelines will be disseminated in the form of a published handbook and through the AUA website. While no specific time frame for reviewing the guidelines is mentioned (Appendix 1), the AUA guidelines panel has in place a panel charged with periodic review of the literature and plans for updating the guidelines based on the importance of contemporary literature.

The strength of the recommendations made in the AUA guidelines was graded by degrees of flexibility using 3 levels, which are summarized in Appendix 2. Appendix 3 summarizes the key recommendations made by the 2007 AUA prostate cancer guidelines that were categorized as “standard.” A section of the guidelines document specifically addresses the issue that the panel was unable to develop guidelines statements other than “options” for a majority of important treatment decisions due to the lack of high quality data. They further conclude that this is unlikely to change in the absence of further RCT evidence.

BAUS Guidelines

The BAUS published guidelines for prostate cancer in conjunction with the Royal College of Radiologists in 1999 and updated those guidelines in 2001.¹² Efforts to update the guidelines document are ongoing but are not expected to be completed until 2008.

The BAUS prostate guidelines are of high methodological quality (Appendix 1). The guidelines document clearly identifies the different organizations involved in the development process and their individual representatives. Besides urologists, these representatives included radiation oncologists, medical oncologists, nurses and palliative care specialists. A detailed timeline of the efforts of the guideline panel is included in the guidelines document. The literature search through 1998 was comprehensive and based on MEDLINE[®] and The Cochrane Library. The search was further supplemented by the hand searching of current journals, cited references and other guidelines documents. While the method of data abstraction is not reported, the BAUS guidelines clearly identify how the quality of evidence and the strength of each recommendation is rated according to AHRQ criteria (Appendix 2). In addition to providing recommendations, the guidelines define quality standards, examples of which are provided (Appendix 4). Like the AUA guidelines, the BAUS guidelines were independently peer reviewed and revised before their release (Appendix 3). The issues of disseminating and implementing these guidelines at a local level are explicitly addressed. In addition, the guidelines provided a target date for publishing a first revision in 2001 which was met. However, no updates have since

been made available, thereby limiting the applicability of this document to contemporary patients with prostate cancer.

EAU Guidelines

The EAU prostate cancer guidelines were first published in 2001 and were updated in 2007.^{13,14} Like the BAUS guidelines, the EAU guidelines include clinically localized and metastatic prostate cancer in their scope. With regard to guidelines methodology, the EAU prostate cancer guidelines follow an approach based on the Delphi principles that is distinctly different from that of the AUA and BAUS. This approach is an iterative process that involves the facilitation of a panel of experts to produce a series of key statements on a chosen subject that are then rated independently and recirculated until there is a sufficiently consistent response to assume a consensus has been reached. However, the EAU guidelines document provides little information about the actual guidelines development process or panel members. There is no information about which sources of information were used to identify the relevant evidence, and whether the literature search was systematic and comprehensive. No information is provided about the data abstraction process and how key recommendations were formulated (Appendix 1). Meanwhile, the EAU guidelines use a transparent system that links quality of evidence to the strength of recommendation, which is the same AHRQ system used by the BAUS.¹⁵ Examples of specific recommendations made by the EAU prostate cancer guidelines are provided in Appendix 3. Like most prostate cancer guidelines, issues of implementation are not specifically addressed.

MOH Guidelines

The MOH guidelines were developed under the auspices of the Singapore National Committee on Cancer Care and published in 2000.¹⁶ Work groups included members from the Singapore Urological Association and the Asian Society of Uro-oncology. While the names of the participating individuals are listed, there is no information about which disciplines they represent. Few methodological details are provided except for the system used to identify the level of evidence and grade the strength of recommendation, which represents a modified AHRQ system (Appendix 2).¹⁵ In addition, so-called good practice points represent the expert opinion of the panel members. Examples of these recommendations are provided in Appendix 3.

NCCN Guidelines

The NCCN is comprised of representatives of the existing 20 National Institutes of Health designated comprehensive cancer centers in the United States. The NCCN has developed clinical practice guidelines for the majority of tumors, including prostate cancer. Clinical practice guidelines are algorithm based and feature pathways that address a clinical spectrum that includes the initial diagnosis of a malignant tumor, its evaluation and staging, primary treatment, adjuvant therapy and salvage/recurrence therapy. Another attractive feature is that they are routinely updated, most recently in April 2007.¹⁷

From a methodological perspective, the NCCN guidelines take a distinct approach by using categories of consensus to grade their recommendations. The quality of evidence is

graded as “high level” or “lower,” and levels of consensus are “uniform,” “non-uniform” and “major disagreement” (Appendix 2). Category 3 recommendations may be based on evidence of any level if the panel experts disagree on the significance of high level trials or whether the findings of such trials can be generalized. All recommendations are level 2A unless otherwise indicated. The NCCN prostate cancer guidelines do not provide information on the sources of evidence, describe the rigor of the data abstraction process or identify the evidence underlying a given recommendation specifically using references (Appendix 1). Specific examples of key recommendations are provided in Appendix 3.

NICE Guidelines

Guidelines for prostate cancer developed by the NICE in the United Kingdom are included in the manual on improving outcomes for all types of urological cancers. The most recent update was provided in 2002.¹⁸ The generation of this report involved a large and diverse group of stakeholders, which are clearly identified. The NICE guidelines apply the Scottish Intercollegiate Guideline Network rating system, and the level of evidence was rated as A, B or C (Appendix 2) and referenced in the text.^{19,20} However, specific recommendations were not rated. The report emphasizes the importance of involving multidisciplinary prostate cancer teams as well as treatment at high volume centers of excellence and specifically identifies certain ongoing clinical trials that patients may be eligible for. The NICE guidelines were independently peer reviewed before release but were not pilot tested. As in most prostate cancer guidelines, methods of dissemination and implantation are not specifically addressed (Appendix 1).

RCSI Guidelines

This guideline document published in 2002 provides few details about the process by which it was developed (Appendix 1).²¹ It uses the same AHRQ rating system for levels of evidence and grades of recommendation as that used by the EAU guidelines.¹⁵ However, these guidelines are notable for providing explicit quality standards for patient care within a given health system (Appendix 4).

CHALLENGES IN PROSTATE CANCER GUIDELINE DEVELOPMENT

We outline the central challenges that organizations vested in the development of prostate cancer guidelines face. There is a paucity of high level evidence in the prostate cancer literature that is provided by appropriately conceived, executed and reported randomized controlled trials, and well designed prospective observational studies.^{22,23} This issue is not easily rectifiable, but will require broad based efforts to raise awareness of the need for better evidence to inform clinical decision making in urology. It is of critical importance that “consumers” of the prostate cancer literature develop an appreciation of inherent potential bias in uncontrolled case series, which form the bottom of the hierarchy of evidence yet represent more than 70% of the urological literature.²⁴ In the absence of high quality evidence it is not surprising that developers of evidence-based guidelines have considerable difficulty making strong recommenda-

tions for or against a given diagnostic or therapeutic intervention.

There is also considerable variability in the methodology by which different organizations develop prostate cancer guidelines as well as shortcomings in the reporting of such methodology. There are major inconsistencies among systems used for grading the quality of evidence and the strength of recommendations as well as a lack of defined processes for how guideline developers move from one to another. These represent a major source of discrepancies in recommendations made in guidelines produced by different developers and ultimately stand in the way of the successful implementation of any evidence-based practice. This issue is not exclusive to prostate cancer, but has been previously recognized as a major hurdle to the acceptance of guidelines by patients and clinicians.⁸

THE GRADE APPROACH TO GUIDELINES DEVELOPMENT

A possible avenue for unifying the guidelines development process is the GRADE approach which has been endorsed by more than 20 leading professional organizations.^{4,5} The GRADE working group was established in 2000 as an informal collaboration of individuals with an interest in tackling the inconsistencies of present grading systems and developing a unified approach.³ Members of many organizations that have previously contributed to developing evidence hierarchy systems, including the AHRQ, National Health and Medical Research Council, NICE and Scottish Intercollegiate Guidelines Network, participated in the GRADE effort with their long-standing experience and helped identify new approaches against the shortcomings of existing guideline methodology. The GRADE approach addresses many important aspects of the guideline development process which relate to the methodological rigor, context and content, and application of the guidelines (see [figure](#)). Besides the World Health Organization, the GRADE approach has been formally adopted by a number of leading organizations such as the American College of Physicians, American College of Chest Physicians and American Thoracic Society.² We provide a brief introduction to the guiding principles of the GRADE approach and demonstrate its applicability to prostate cancer. While representing only one of several methodological approaches to evidence-based guideline development, it provides an excellent example of how key issues can be addressed in a balanced and transparent manner.

Strength of Recommendation

The GRADE system uses a simplified approach that categorizes recommendations as strong or weak. Recommendations can be for or against an intervention. The strength of any recommendation hinges on 2 factors, that is the quality of the evidence regarding a treatment effect, and the trade-off between desirable and undesirable effects, ie benefit and harm. Within this framework a strong recommendation indicates that the trade-off is clear enough that most patients, despite differences in values, would make the same choice. A weak recommendation indicates that the trade-off is less clear and that individual patient values may lead to different choices. Importantly, strong recommendations are not necessarily linked to high quality evidence. For example, prostate cancer guideline developers applying the GRADE

system would likely formulate a strong recommendation for immediate androgen ablation to treat patients with hormone naïve metastatic prostate cancer suffering from impending spinal compression, despite the lack of high quality evidence. In this case large and consistent treatment effects observed in case series provide compelling evidence to support a strong recommendation. Thus, the trade-off between benefit and harm clearly favors one over the other.

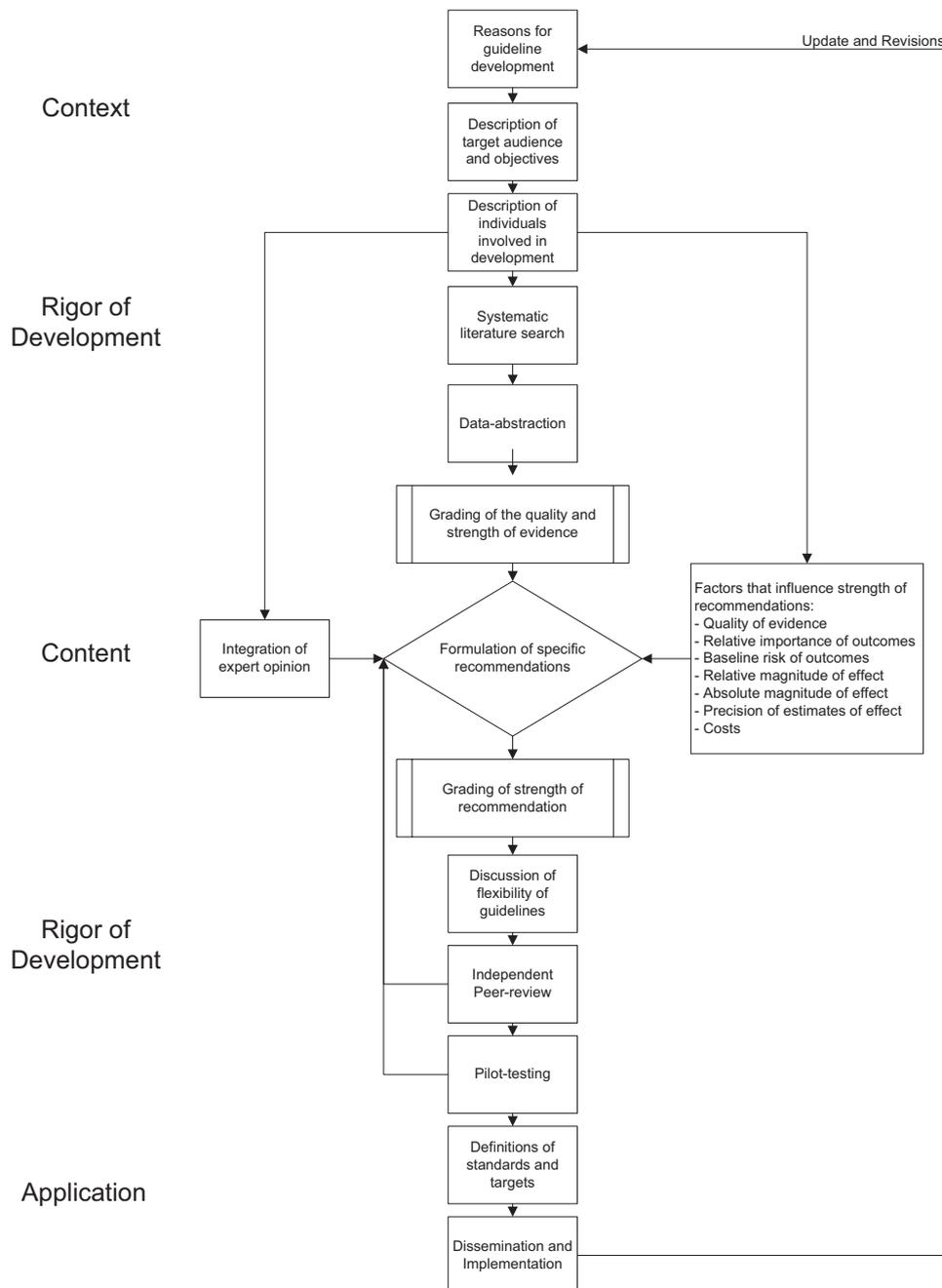
Quality of Evidence

Many systems that are currently being used to grade the quality of evidence rely primarily on the basic study design (ie randomized control trial or prospective cohort study with a comparison group) for determination and place systematic reviews at the top of the hierarchy while ignoring the quality of the underlying studies. However, randomized controlled trials that fail to use methodological safeguards against bias such as concealed allocation, blinding, completeness of followup and intent-to-treat analysis provide weaker evidence and should be downgraded.^{25,26} Systematic reviews and meta-analyses are only as good as the individual RCTs that are included, and need to follow strict methodological criteria to be considered high quality evidence. Methodological standards for the reporting of RCTs, systematic reviews and meta-analyses have been developed by the CONSORT (Consolidated Standards for Reporting Trials) and Quality of Reporting of Meta-Analyses groups, respectively.^{27,28} To date European Urology is the only major urological journal to have endorsed the CONSORT guidelines.

To determine study quality the GRADE system captures multiple dimensions that affect the confidence we place in the results of studies that address a given question.^{2,29} It uses 4 categories of quality of evidence which are “high,” “moderate,” “low” and “very low.” The strongest evidence comes from 1 or more well designed and well executed randomized control trials yielding consistent, directly applicable results. As discussed, under certain circumstances strong evidence can also come from observational studies that yield large effect sizes. The moderate strength category is occupied by randomized trials with important limitations (ie lack of allocation concealment, failure to blind the outcome assessors) and by exceptionally strong observational studies. Observational studies without important risk of bias and, on occasion, RCTs with multiple serious limitations fill the low quality evidence category. Observational studies with important methodological limitations, such as small case series or other observational studies that are prone to bias fill the very low quality category. This categorization follows the principle that all relevant clinical studies provide evidence, the quality of which may vary. In that way the GRADE system is more flexible than many other systems because it allows guideline developers to integrate lower level evidence without compromising the quality of a recommendation.

Factors That Affect the Strength of a Recommendation

Besides the quality of evidence, the GRADE approach makes other explicit determinations about several factors that influence the strength of a recommendation (see [figure](#)). These include the relative importance of the outcomes, baseline risk of outcomes, magnitude of the relevant risk, absolute



Flow diagram of recommended guideline development process

magnitude of the effect, precision of the estimates of the effect and costs. Relative and absolute risk reductions may relate to the benefits, harms and other burdens (ie costs, time afforded to receive treatment), and are reported in relationship to an alternative intervention (ie radical prostatectomy vs active surveillance to treat low risk prostate cancer). Large relative and absolute risk reductions are more likely to lead to strong recommendations than are small effect sizes. Also, guideline developers should consider the magnitude of the net effect. Large relative effects will more likely lead to a strong recommendation if the balance of benefit, harm and burden go in the same direction. What members of a guideline panel would consider a large effect size would require a value judgement about the relative value of a given outcome. For example, prostate cancer

guideline developers would certainly place the risk of prostate cancer related death at a higher importance than the risk of treatment related erectile dysfunction. While such judgements make sense intuitively and are already finding their way into existing guidelines, the GRADE approach seeks to make these determinations transparent and explicit. Prostate cancer guidelines should further consider patient baseline risk and make separate recommendations for populations at different risks. This approach is exemplified by the different risks of prostate cancer specific death when choosing conservative management and stratified by Gleason score. The risk categories described by D'Amico et al that are used by the NCCN guidelines reflect the recognition of such differences in baseline risk.³⁰ Finally, important benefits should come at a reasonable cost. With all else being

equal the higher the incremental costs, the less likely it is that guideline developers will formulate a strong recommendation.

CONCLUSIONS

Clinical practice guidelines have been developed by a number of leading organizations using different methodologies. Specifically, discrepancies exist in the criteria used to grade the quality of evidence and to categorize the strength of recommendations. Such differences are the likely source of conflicting recommendations which may undermine public confidence in the principles of evidence-based practice and ultimately stand in the way of an evidence-based management of prostate cancer. There appears to be a need to standardize the processes used by

leading urological organizations to develop clinical guidelines for the management of prostate cancer. The GRADE approach provides an example of a methodologically rigorous yet practical system to develop clinical practice guidelines. Adoption of a unified approach to prostate cancer guideline development by leading organizations is expected to offer considerable rewards in terms of efficiency, guideline credibility, and optimal clinical decision making to patients and health care providers alike. Furthermore, there is a critical need for more methodologically rigorous prospective studies that provide high level evidence in prostate cancer. Professional organizations such as the AUA and EAU are expected to have an important role in raising the awareness of this issue and promoting the career development of young individuals that are vested in conducting high quality research.^{31,32}

APPENDIX 1

Methodological characteristics of prostate cancer guidelines							
	AUA	BAUS	EAU	MOH	NCCN	NICE	RCSI
Rigor of Development Process							
Is there a description of the individuals who were involved in the guidelines development group?	✓	✓			✓	✓	
Did the group contain representatives from all key disciplines?	✓	✓			✓	✓	
Is there a description of the sources of information used to select the evidence on which the recommendations are based?	✓	✓					
Is the evidence used identified by citation and referenced?	✓	✓	✓	✓			✓
Is the method of data abstraction specified?							
Were the guidelines independently reviewed prior to publication/release?	✓						
Were the guidelines piloted?	✓	✓			✓	✓	
Context and Content							
Are the objectives of the guidelines clearly defined?	✓	✓		✓	✓	✓	✓
Are the recommendations graded according to the strength of the evidence?		✓	✓	✓		✓	✓
Is there an explicit statement of how the patient's preferences should be taken into account (flexibility)?	✓	✓				✓	
Is there an estimate of the costs or expenditures likely to incur from the recommended management?							✓
Application of Guidelines							
Does the guideline document suggest possible methods for dissemination and implementation?	✓	✓					
Does the guideline document identify clear standards or targets?		✓					✓
Is there a mention of a date for reviewing or updating the guidelines?*		✓			✓		

* Guidelines were identified as having met this criterion only if an explicit date (ie specific year) or time-frame (ie 2 years) was provided

APPENDIX 2

Grading system for the quality of evidence and strength of recommendation used by different prostate cancer guidelines		
Organization (Year)	Grading of Evidence Quality	Grading of Recommendation
AUA (2007) ¹¹	No information provided	3 Levels of Flexibility: ³¹ Standard: A guideline statement is a standard if: (1) the health outcomes of the alternative interventions are sufficiently well known to permit meaningful decisions, and (2) there is virtual unanimity about which intervention is preferred. Guideline: A guideline statement is a recommendation if: (1) the health outcomes of the alternative interventions are sufficiently well known to permit meaningful decisions, and (2) an appreciable but not unanimous majority agrees on which intervention is preferred. Option: A guideline statement is an option if: (1) the health outcomes of the interventions are not sufficiently well known to permit meaningful decisions, or (2) preferences are unknown or equivocal.
BAUS (1999) ¹²	AHRQ Levels of Evidence ³² 1a – Meta-analysis of RCTS 1b – At least one RCT 2a – One well-designed study without randomization 2b – At least one other type of well-designed, quasi-experimental study 3 – Well-designed non-experimental studies, such as comparative studies, correlation studies and case reports 4 – Expert committee report of opinions or clinical experience of respected authorities	AHRQ Grades of Recommendation: ³² A – Based on clinical studies of good quality and consistency addressing the specific recommendation and including at least one RCT B – Based on well-conducted clinical studies, but without RCTs C – Made despite the absence of directly applicable clinical studies of good quality
EAU (2005) ¹³	AHRQ Levels of Evidence also used in BAUS guidelines (see above) ³²	AHRQ Grades of recommendation also used in BAUS guidelines (see above) ³²
MOH (2000) ¹⁶	AHRQ Levels of Evidence also used in BAUS guidelines (see above) ³²	Modified AHRQ Grades of Recommendation: ³² with addition of Good Practice Points (GPP) defined as best practice based on the clinical experience of the guideline development group
NCCN (2007) ¹⁷	High – defined as “high-powered randomized clinical trials or meta-analysis” Lower – “broadly interpreted” and ranging from “. . . phase II or large cohort studies to individual practitioners’ experience”	Category of Consensus 1 – High level evidence and uniform consensus 2A – Lower level evidence but uniform consensus 2B – Lower level evidence non-uniform consensus 3 – Any evidence and major disagreement
NICE (2002) ¹⁸	SIGN rating system ¹⁹ A – RCTs or systematic reviews of RCTs B – Non-randomized controlled trials or observational studies C – Professional consensus	Recommendations not graded
RCSI (2002) ²¹	AHRQ Levels of Evidence also used in BAUS guidelines (see above) ³²	AHRQ Grades of Recommendation also used in BAUS guidelines (see above) ³²

APPENDIX 3

Examples of specific recommendations made in prostate cancer guidelines by different organizations

Guideline	Year	Grade	Recommendation
AUA ¹¹	2007	Standard	<ul style="list-style-type: none"> • A patient with clinically localized prostate cancer should be informed about the commonly accepted initial interventions including, at a minimum, active surveillance, radiotherapy (external beam [EBRT] and interstitial radiation therapy) and radical prostatectomy (RP). A discussion of the estimates for benefits and harms of each intervention should be offered to the patient.
		Standard	<ul style="list-style-type: none"> • Patient preferences and health conditions related to urinary, sexual and bowel function should be considered in decision making. Particular treatments have the potential to improve, to exacerbate or to have no effect on individual health conditions in these areas, making no one treatment modality preferable for all patients.
		Standard	<ul style="list-style-type: none"> • When counseling patients regarding treatment options, physicians should consider the following: <ul style="list-style-type: none"> – Two RCTs show that higher dose radiation may decrease the risk of prostate specific antigen (PSA) recurrence; – Based on outcomes of one RCT, when watchful waiting (WW) and RP are compared, RP may be associated with a lower risk of cancer recurrence, cancer-related death and improved survival.
		Standard	<ul style="list-style-type: none"> • For patients choosing active surveillance, the aim of the second-line therapy (curative or palliative) should be determined and follow-up tailored accordingly.
		Standard	<ul style="list-style-type: none"> • Patient preferences and functional status with a specific focus on functional outcomes including urinary, sexual, and a bowel function should be considered in decision making.
		Standard	<ul style="list-style-type: none"> • When counseling patients regarding treatment options, physicians should consider the following: <ul style="list-style-type: none"> – Based on outcomes from one RCT, the use of neo-adjuvant and concurrent hormonal therapy for a total of six months may prolong survival in the patient who has opted for conventional dose EBRT; – Based on outcomes of one RCT, when WW and RP are compared, RP may be associated with a lower risk of cancer recurrence, cancer-related death and improved survival.
BAUS ¹²	2001	A	<ul style="list-style-type: none"> • Neoadjuvant or adjuvant hormone therapy should be considered for patients with locally advanced (T3-4) disease who are to be treated with radical radiotherapy.
EAU ¹³	2007	A	<ul style="list-style-type: none"> • Hormonal treatment for stage T1a is not an option.
		A	<ul style="list-style-type: none"> • For stage T1b-T2b, RP is the standard treatment for patients with a life expectancy > 10 years who accept treatment-related complications.
		A	<ul style="list-style-type: none"> • For stage T1b-T2b, pure anti-androgens are associated with poorer outcome compared to watchful waiting and are not recommended.
		A	<ul style="list-style-type: none"> • For stage T1b-T2b, NHT + radiotherapy have no proven benefit.
		A	<ul style="list-style-type: none"> • For stage T1b-T2b, hormonal (2-3 years) + radiotherapy is better than radiotherapy alone for poorly differentiated tumors.
		A	<ul style="list-style-type: none"> • For stage T3 with a life expectancy > 5-10 years, dose escalation > 70 Gy seems to be of benefit. If it is not available, a combination with hormonal therapy could be recommended.
		A	<ul style="list-style-type: none"> • Hormonal treatment is better than watchful waiting for symptomatic patients, extensive T3-T4, high PSA level (> 25 ng/ml), unfit patients.
		A	<ul style="list-style-type: none"> • For stage T3-T4, radiotherapy + hormonal treatment seems better than radiotherapy alone.
		A	<ul style="list-style-type: none"> • For stage N+ / M0, standard hormonal therapy is recommended.
		A	<ul style="list-style-type: none"> • For stage M+, standard hormonal therapy is recommended. Symptomatic patients should not be denied treatment.
MOH ¹⁶	2000	A	<ul style="list-style-type: none"> • Population screening for prostate cancer among Asians is not recommended.
		A	<ul style="list-style-type: none"> • Prostate biopsy is recommended for patients with abnormal PSA results and/or suspicious digital rectal examination.
		A	<ul style="list-style-type: none"> • Hormonal therapy remains the mainstay of treatment for metastatic prostate cancer. Surgical castration is equal in efficacy compared with other means of medical castration, including total androgen blockade.
		A	<ul style="list-style-type: none"> • None of the second line treatment options has shown consistent advantage. The choice of treatment should again be individualized.
NCCN ¹⁷	2007	Category 1	<ul style="list-style-type: none"> • Androgen deprivation therapy (at least 2 years) and 3-dimensional radiation therapy is a treatment modality for patients at high risk for recurrence (T3a or Gleason score 8-10 or PSA >20 ng/ml)
		Category 1	<ul style="list-style-type: none"> • Androgen-deprivation therapy (at least 2 years) and 3-dimensional radiation therapy is a treatment modality for patients at very high risk for recurrence (T3b-T4)
RCSI ²¹	2002	A	<ul style="list-style-type: none"> • Combined androgen blockade should not be used routinely on current evidence.
		A	<ul style="list-style-type: none"> • Neoadjuvant or adjuvant hormone therapy should be included in the protocol for high-risk patients with localized prostatic tumors.

APPENDIX 4

Examples of specific standards made in prostate cancer guidelines by the BAUS and RCSI guidelines

Guideline	Year	Standard
BAUS ¹²	2001	<ul style="list-style-type: none"> • Documented pre-testing counseling should have been undertaken in >90% of asymptomatic men diagnosed on the basis of PSA. • All patients considered to be fit for radical therapy should be counseled regarding the options; it should be documented that such counseling has taken place. • Less than 5% of patients should have incontinence severe enough at one year to require more than 2 pads a day, an appliance or to warrant consideration for an artificial sphincter. • All patients undergoing total prostatectomy should be followed up in a specialist unit, and data should be collected regarding clinical pathological status, survival, local control and morbidity. • Following radical radiotherapy of the prostate, the incidence of severe late normal tissue damage should be less than 5% at 2 years.
RCSI ²¹	2002	<ul style="list-style-type: none"> • Less than 3% of patients should be wet to such degree at 1 year as to require multiple pads or implantation of an artificial sphincter. • Patients should be followed in a specialized urology department. Data relating to quality of life detected clinical recurrence rate, recurrence rate by PSA or imaging, survival rates and complications can thereby be recorded and analyzed. • Following radical radiotherapy of the prostate, the incidence of severe late complications (beyond 90 days) to bladder and rectum should be less than 5% at 2 years. • Patients undergoing radical radiotherapy should be followed by a specialist unit. Data regarding quality of life, survival, local and distant recurrence, and morbidity can thereby be recorded.

Abbreviations and Acronyms

AHRQ	=	Agency for Health Care Policy and Research
AUA	=	American Urological Association
BAUS	=	British Association of Urological Surgeons
EAU	=	European Urological Association
GRADE	=	Grading of Recommendations, Assessment, Development and Evaluation
MOH	=	Singapore Ministry of Health
NCCN	=	National Cancer Center Network
NICE	=	National Institute for Health and Clinical Excellence
PSA	=	prostate specific antigen
RCSI	=	Royal College of Surgeons in Ireland
RCT	=	randomized controlled trial

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EDITORIAL COMMENTS

As a general principle, guidelines can be divided into the 2 categories of more narrow, or focused, guidelines (ie treatment of localized prostate cancer) and more broad based guidelines that cover a much wider field (ie prostate cancer). The future method for producing guidelines suggested by the authors (the GRADE methodology) may well serve the purpose for guidelines with a narrow perspective where it is possible to judge the articles one by one. The method is time and resource consuming but will probably give a reliable result for these types of narrow questions/guidelines.

However, if the aim is to present a frequently updated, broad clinical practice guideline, the use of such an elaborate methodology is directly counterproductive. The resources involved to evaluate all new literature about prostate cancer, not to mention the whole field of urology, exceed what most professional organizations can provide. The rigor of the methodology would become the “rigor mortis” of the process.

All guidelines produced to date include evaluation of the underlying evidence (ie scientific articles) and writing by experts in the field. Thus, the key question is how much difference there is in the end product (the guideline) based on this structured search compared to a narrow search for RCTs by experts in the field with knowledge of the current literature. If one does not have large resources, I seriously doubt that the eventual difference is worth the effort. Guidelines can never replace the art of medicine, irrespective of how rigorous the methodology.

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The authors present a review of the current guidelines for localized prostate cancer. What is clear is that for this disease process, as for several others within the domain of urological disease, no unanimity of opinion exists as to what evidence should be included, how that evidence should be analyzed and how recommendations can be derived from that evidence. Several groups have suggested methodologies to enhance and standardize evidence analysis and review, and it is generally hoped that we avoid the veritable “Babel” that has been experienced in the quality of life assessment of urological disease (reference 28 in article).¹ Even methods to stratify and categorize overall recommendations are still in flux (reference 29 in article). This discourse is a microcosm of a global debate now raging about the extant evidence and how best to translate this experience to improved clinical practice, that is how best to draw meaningful conclusions which will improve clinical care and ensure patient safety.

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of evidence and strength of recommendations in ATS guidelines and recommendations. *Am J Respir Crit Care Med* 2006; **174**: 605.

REPLY BY AUTHORS

While the methodological framework for the development of clinical practice guidelines has evolved considerably during the last decade, as witnessed by the AGREE statement (reference 7 in article), there is no unanimity of opinion. Consequently the evolutionary process of guideline development is still in its “Jurassic Period.” While the methodological rigor that is essential to high quality, contemporary evidence-based guidelines may be viewed by some as coming at the risk of inducing “rigor mortis,” we respectfully disagree with this assessment and argue strongly that the guideline process is “not dead yet.” In fact, it is alive and well, and the future is bright,

Questions remain as to how to best grade the quality of the evidence, balance benefit and harm, incorporate patient values and preferences, and develop recommendations that will be useful to urologists at the point of care. While the approach that has been developed by the GRADE group may only be one of several, it is gaining considerable traction in other areas of medicine as a practical solution to many issues that guideline developers face. In fact, an announcement at the 2008 annual meeting suggests that the AUA may follow this lead by endorsing a modified version of the GRADE approach that was developed in conjunction with the American College of Chest Physicians (reference 29 in article). This development is driven by the public expectation of a guideline development process that is methodologically stringent and transparent. The stakes for clinical practice guidelines appear particularly high at a time when these are becoming the basis for the development of quality of care measures that are likely to directly impact urologists’ reimbursement in the future.¹ A certain amount of rigor in the guideline development process may therefore be “de rigueur.”

As guideline developers across the globe engage in controversial debates about the best possible approach to guideline development, it is important to recognize that we all share the common goals of improving patient outcomes and ensuring quality of care. Guideline development by individual groups or organizations with limited resources in isolation may truly place us in a situation of “caveat emptor.” Joint guideline development would allow the concept of an economy of scale to apply, and should be viewed as a tremendous opportunity for international collaboration to build consensus, avoid duplication of effort and reduce cost. Therefore, as the clinical practice guidelines process continues to evolve, we must be willing to embrace the challenges of an evidence-based framework that is evolutionary and revolutionary as we strive to achieve the stated goal of improving the quality of care for patients with urological diseases.

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