Archives of Surgical Oncology

Huebner and Barqawi, Arch Surg Oncol 2015, 1:1
DOI: 10.4172/2471-2671.1000106

Review Open Access

The Risks and Benefits of Current Treatment Options for Prostate Cancer and Future Possibilities in Advanced Imaging and Targeted Therapy – A Review

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Received date: Nov 10, 2015; **Accepted date:** Dec 26, 2015; **Published date:** Dec 30, 2015

Background

242,000 cases of prostate cancer are diagnosed annually, rendering it the most common noncutaneous cancer and the second highest cause of cancer death among men [1]. However, the majority of prostate cancers are indolent in progression, and the risk of cancer-specific mortality is just 3.7% [1,2]. The incidence and mortality of prostate cancer are largely inconsistent, and the advent of PSA screening has contributed to overdiagnosis and overtreatment [3,4]. Overdiagnosis can be defined as the detection of prostate cancer during screening that would not have been clinically diagnosed throughout a man's lifetime in the absence of screening [5]. PSA testing can identify disease 6 to 13 years before it presents clinically, and therefore overdiagnosis is a substantial consequence, especially because prostate cancer is generally diagnosed in older men [2,5,6]. 10-56% of tumors never lead to clinical symptoms, and detection of prostate cancer during autopsy studies has been reported as high as 60-70% [7,8].

Based on Microsimulation Screening Analysis, 98 men would need to be screened and 5 cancers detected in order to prevent one prostate cancer-specific death [5]. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial found no significant difference in mortality between individuals undergoing organized annual screening and those undergoing opportunistic screening at 13 years follow-up, despite annual screening resulting in a 12% relative increase in prostate cancer diagnoses [9]. This increase is representative of the problem created by overdiagnosis in the era of PSA screening; more cancers are detected, but no more lives are saved.

The levels of overdiagnosis and overtreatment are widely variable, with overdiagnosis estimates ranging from 1.7% to 67% of cases detected by PSA screening [10]. Nonetheless, the unspecific nature of PSA screening inhibits physicians from determining which patients will progress to fatal disease [2,7,11]. The growing prevalence of unilateral pT2a and pT2b prostate cancers is partially attributable to the role of PSA screening in the trend toward earlier diagnosis and intervention, which has resulted in profound stage migration [12]. In fact, evidence shows that the introduction of PSA testing has led to the systematic reclassification of Gleason scoring, resulting in a superficial improvement in clinical outcomes [13,14]. As Gleason scores are the most powerful indication of prognosis and treatment recommendation, their reclassification has established a lower PSA threshold for biopsy and has promoted the performance of repeat biopsies for negative findings, resulting in overdiagnosis and overtreatment [15,16]. Annual PSA screening for prostate cancer was given a level D recommendation by the US Preventative Health Task Force in 2011, resulting in a 28% decline in incident diagnoses of low, intermediate, and high-risk prostate cancers in the following year, most significantly in men over the age of 50 [17,18]. While the recommendation may have reduced the rate of overdiagnosis, especially in older cohorts with higher comorbidities, it may have also caused more aggressive cancers to be overlooked. Both overtreatment of low-risk disease (PSA≤10 ng/mL, Gleason score ≤6, T1a-c or T2a tumor) and undertreatment of high-risk disease (PSA>20 ng/mL or Gleason score 8-10 or T2c tumor) are evident in current treatment patterns, warranting the development of new molecular and genetic indicators and imaging techniques for more precise detection of disease progression [8,15,19]. The purpose of this article is to provide an extensive review of current diagnostic tools and treatment options for prostate cancer and to outline how the standard of care is changing to meet new developments in clinical and translational research.

Review of the Literature

PSA screening

Prostate cancer is not the only cause of elevated PSA serum levels; high PSA can also be associated with the three most common prostatic diseases – prostatitis, BPH, and prostate cancer – as well as physical activity, infection, and medication, the latter of which can also suppress PSA levels [20]. Despite these complications, PSA concentration has been strongly correlated with prostate cancer metastasis 25-30 years after screening, suggesting that early testing is useful for identifying patients with the highest risk [21,22]. Vickers et al. [22] reports a 15-year risk of prostate cancer metastasis to be 0.09% from ages 45-49 and 0.28% from ages 51-55, supporting the conclusion that just three lifetime PSA tests would be sufficient for detecting clinically significant cancer in at least 50% of the male population. The cost-effectiveness of the screening diminishes in older patients due to loss of quality of life from overdiagnosis; data suggest that over the age of 60, only patients with PSA levels >2 ng/mL would benefit from continued screening [23,24]. In a sampling of men with nonmetastatic prostate cancer from the Prostate Cancer Outcomes Study, Daskivich et al. [25] documented an other-cause mortality rate of greater than 50% for those with multiple comorbidities over the age of 60. At 14 years, prostate cancer mortality was 5% for men with low-risk disease and 23% for men with high-risk disease. These data suggest that older men with localized prostate cancer diagnoses should consider conservative management to maintain maximum quality of life, given the likelihood of non-cancer related death.

PSA doubling time has been used as an indication of biochemical failure in patients initially under active surveillance. A 99.3% prostate cancer specific survival rate at 8 years post-diagnosis was reported in patients initially under active surveillance but who were offered

curative treatment if PSA levels doubled within 3 years. These results suggest that selective delayed intervention based on PSA doubling time will result in about 70% of patients remaining stable or having slow, clinically insignificant progression with no need for radical treatment [11]. While this approach has potential, it currently remains to be an uncertain predictor in determining the need for radical intervention.

Curative treatment

The effectiveness of curative treatments such as radical prostatectomy, external beam radiation, and brachytherapy is not entirely clear. The risk of recurrence after radical prostatectomy in particular is highly variable. Despite intervention by radical prostatectomy, a PSA level increase of >2.0 ng/mL in the year before prostate cancer diagnosis was reported to be indicative of prostate cancer-specific mortality [26,27]. Radical prostatectomy has been shown to decrease all-cause mortality if PSA>10 ng/mL and has yielded a 6% reduction in bone metastases 8 years post-treatment, but no significant benefit is evident if PSA≤10 ng/mL; in fact, up to a 4% greater mortality was observed in radical prostatectomy patients with PSA≤10 ng/mL when compared to those under observational management [7,16]. In patients with PSA levels of at least 19.7, a retrospective study of prostate cancer patients treated by external-beam radiation therapy reported less than 50% biochemical cancer-free survival rate [28]. Therefore, in both low-risk and high-risk cancers, radical intervention has not been shown to consistently produce successful outcomes.

A study of pre-PSA era prostate cancer treatment in patients under the age of 65 did show a reduction in prostate cancer-specific mortality rate 15 years post radical prostatectomy (14.6%) in contrast to a 20.7% rate in patients managed under a watchful waiting program [29]. However, because these cancers were not detected by PSA screening, it is likely that there was a greater extent of more clinically advanced cancers in the cohort that was studied. The insignificance of mortality reductions by radical intervention observed in the Prostate Cancer Intervention versus Observation Trial (PIVOT) study reflect in part the more favorable prognosis of patients with tumors detected by PSA screening. The resulting lead time and increased rates of overdiagnosis have led to a greater number of low risk, clinically insignificant tumors that naturally yield better outcomes [16,30].

While prostate cancer-specific mortality is not necessarily hindered by radical intervention, data suggest that these treatments do impair quality of life. Multiple studies, including data from the U.S. CaPSURE registry, have shown that radical prostatectomy patients are more likely to suffer from urinary incontinence than radiotherapy patients and are also more likely to have higher rates of impotency, although both groups report high erectile dysfunction rates (62-94%) [31-34]. Complications related to bowel function affect individuals treated by both radical prostatectomy and radiotherapy, but radiotherapy patients have been indicated to experience more significant declines [32-34].

While these deteriorations in quality of life are significant, it is important to compare them with age-adjusted normative data. In a study of older men (median age 72.5) without prostate cancer, approximately a third reported urinary leakage, a third rectal dysfunction, and almost two-thirds erectile dysfunction [35]. These findings emphasize the importance of comparing functional outcomes of prostate cancer patients with controls of the same age. However, multiple studies have revealed that while no significant difference in overall health-related quality of life exists between prostate cancer patients who have undergone radical prostatectomy and age-adjusted controls, the sexual, bowel, and urinary functions of radical prostatectomy patients have declined more substantially than that of controls [36-39]. Multi-model treatment and particularly the use of androgen deprivation therapy have been associated with the highest risk of adverse effects and the greatest impairment to physical function [34,39,40].

Some functional stabilization is evident in the recovery process, with those experiencing early functional impairment from radical prostatectomy or brachytherapy reporting a return to baseline, with the exception of sexual function, within 2 years of treatment [41]. Other findings, however, have indicated consistent functional declines in urinary and sexual function 5 years post-treatment, despite some evidence of stabilization between 2 and 5 years [31]. These conclusions designate the importance of long-term follow-up data in fully assessing functional outcomes of aggressive and conservative treatment modalities for prostate cancer.

Active surveillance

Data from the PIVOT study provide long-term results and strong support for the effectiveness of active surveillance, in which curative treatment is delayed until cancer progression is detected. PIVOT results did not show a significant difference in the number of prostate-cancer specific deaths between radical prostatectomy patients and patients under observation [16]. Multiple studies have reported 94-99% 10-year cancer-specific survival rates in men under active surveillance for low-risk and intermediate-risk prostate cancer, compared to the 90% rate reported for a similar cohort treated by radical prostatectomy [42-45]. There is no difference in overall survival rates between patients who remain on surveillance and those who seek deferred treatment [46]. Annual mortality rates of low-grade prostate cancer patients under active surveillance have been reported to remain stable at 15 years post-diagnosis, and similar or better health-related quality of life outcomes have been documented for those in watchful waiting programs when compared to controls [13,47]. The most common cause of death among active surveillance patients is cardiovascular disease, and the relative risk of non-prostate cancer related mortality has been calculated to be 10 times more likely than death due to prostate cancer [46]. The low risk of prostate-cancer specific mortality suggests that radical intervention in the case of low-grade prostate cancers may not be warranted, despite the prevalence of aggressive therapies such as radical prostatectomy in the U.S. today [19].

Regardless of the compelling evidence for the utilization of conservative management, data reviewed from the U.S. CaPSURE registry revealed that just 6.8% of men with biopsy-proven prostate cancer choose to follow an active surveillance treatment plan, in comparison to 49.9% who elect to undergo radical prostatectomy, 11.6% external-beam radiation therapy, 14.4% primary androgen deprivation monotherapy, and 13.3% brachytherapy. Risk assessment and the physician's recommendation to the patient have been identified as critical reasons behind treatment selection [48]. Of those who choose active surveillance, as many as 50% switch to deferred treatment after 3-5 years, and only 40% undergo a repeat biopsy at 12 months. This lack of adherence demonstrates the need for the development of alternative biomarkers to decrease morbidity. Reduction in the variability of active surveillance enrollment criteria and continual encouragement of patients to follow their observational management programs is also needed in order to increase utilization of active surveillance programs [51,49]. Active surveillance is an

underused treatment strategy in part because healthcare providers do not consistently discuss it as a treatment option, or clinicians present it in a negative way. Discouragement from electing active surveillance has compelled patients and their care providers to pursue more aggressive treatment modalities [2,48,50]. A review of decision aids specific to the treatment of prostate cancer, 8 of which were developed in the U.S., found none to meet International Patient Decision Aid Standards. Some of the aids failed to address active surveillance as a treatment option or the risk of overtreatment when selecting more radical intervention [51]. This problem is not necessarily prevalent in healthcare systems outside of the United States. In comparison to U.S. data, a Swedish study reported that 59% of very low-risk and 41% of low-risk prostate cancer patients opted for active surveillance from 1998-2011, suggesting that overtreatment is beginning to decline internationally [48].

The lack of election and adherence to active surveillance in the U.S. is indicative of the observed patterns in overtreatment of low-risk disease, but undertreatment of high-risk disease has also been identified [7,19,52]. The 10-year cancer specific survival rate for prostate cancer patients treated by initial observational management for poorly differentiated disease (Gleason score 8-10) was reported to be 58-74%, suggesting that this group would have benefited appreciably from more aggressive treatment modalities [42]. The absence of biomarkers for disease aggressiveness prevents the development of active surveillance as a treatment option for low-risk prostate cancer. The ambiguity that exists in distinguishing between clinically significant and insignificant cancers has compelled physicians and their patients to resort to more radical treatment options in order to prevent undertreatment.50 The patterns of overtreatment and undertreatment have established the need for the development of more moderate treatment modalities that lie between observational management and radical intervention in the continuum of prostate cancer management.

Future Treatment Modalities

Targeted focal therapy

The development of targeted focal therapy (TFT) shows promise in bridging the gap between active surveillance and more aggressive therapies. With respect to prostate cancer, TFT has been defined as the use of a minimally invasive technique to ablate all clinically significant cancer foci in the prostate [7,53,54]. The increasing diagnoses of unilateral prostate cancer, in part due to PSA screening, has allowed for augmented use of novel focal ablative therapies. The number of focal treatments per year has increased from 46 in 1999 to 567 in 2007 [12,55]. Ablative options for focal treatment include cryotherapy, brachytherapy, radiotherapy, thermotherapy, and high intensity focused ultrasound (HIFU) [2]. HIFU has yielded a 92% negative biopsy rate post-treatment in low-risk prostate cancer patients [56].

Advancement in imaging technology has allowed for the development of focal cryotherapies that have produced higher erectile function and equivalent biochemical recurrence survival rates at 60 months when compared to whole-gland cryoablation [53,56,57]. Partial gland cryoablation has yielded 75.7% to 84% biochemical recurrence-free rates, 98.4% to 100% urinary continence, 86% sexual potency, and 75% negative biopsies [55,58,59]. While cryotherapy is a more expensive surgical procedure than radical prostatectomy, the overall direct costs of cryotherapy ($9,195) are less than radical prostatectomy ($10,704), due to shorter hospital stays, lack of pathologic costs, and the absence of the need for blood transfusions [60].

No universally accepted biochemical definition has been developed for follow-up protocol after cryotherapy, but the achievement of PSA nadir <0.1 ng/mL has yielded the lowest incidence of biochemical failure within 18 months of cryosurgery [61]. CaPSURE data indicate that just 4.0% of prostate cancer patients elect for cryoablation; long-term follow-up data from additional studies of TFT are needed in order to determine proper patient selection and increase the utilization of focal ablation, but TFT already holds promise as a pragmatic approach for treating low-risk prostate cancer [19,54].

Diagnostic imaging

A crucial influence in the advancement of targeted focal therapy is the improvement of prostate imaging. Transrectal ultrasound (TRUS), the most commonly utilized imaging modality in prostate biopsies, has a 14.3% false-negative rate and tends to undersample the anterior zone, apex, and anterolateral horn of the prostate [53,62-64]. Gleason scores obtained from TRUS biopsy agree with radical prostatectomy specimen Gleason scores only 28.7% of the time [65]. Recent studies have advocated for implementation of endorectal magnetic resonance imaging (MRI) in the assessment of patient eligibility for active surveillance. Clear tumor visualization on prostate MRI is predictive of Gleason score upgrades on confirmatory biopsies [66].

The introduction of 3-dimensional mapping biopsy (3DMB) has also displayed a substantial advancement in the evaluation of prostate cancer. A 3DMB study revealed that 61.1% of all patients and 50% of low-risk patients with unilateral prostate cancer diagnosed by TRUS biopsy actually had bilateral disease [67]. The utilization of 3DMB in the treatment of patients with TRUS biopsy-confirmed early-stage, organ confined prostate cancer yielded a Gleason score upgrade and up-stage in 27.2% and 45.6% of all cases, respectively [62]. 3DMB has the potential to omit a significant number of patients from active surveillance programs and in doing so avoid cases of undertreatment. This improvement in imaging will provide physicians with greater confidence and assurance when assessing the most pragmatic course of treatment for their patients.

The development of 3DMB and focal ablative therapies are helping to elucidate the distinction between mortal and non-mortal prostate cancers. These improvements have lead to the establishment of risk-stratified protocols that will avoid both overtreatment and undertreatment tendencies. The advancement of imaging technology is a crucial factor in eliminating the uncertainty that surrounds the treatment selection process and in increasing the utilization of active surveillance and less aggressive treatment modalities for the maximization of patient quality of life. Improved imaging and targeted biopsy techniques are also essential for the success of molecular profiling of prostate cancer. As cancer treatment progresses towards more personalized therapies, molecular classification of malignant tumors will ensure detection of more aggressive lesions that may be independent of initially detected low-grade cancer [68].

Genomic testing

Genomic testing is a prospective technique for clarifying the metastatic and local invasive potentials of individual tumors, while epigenetic alterations and selective modulation of microRNAs also hold therapeutic potential for all urologic cancers [26,69,70]. Data suggest that the addition of genomic information to traditional

diagnostic variables does yield some improvement in prognostic accuracy [26]. Current approaches include the identification of molecular alterations of prostate cancer in order to develop clinically available expression profiling data for future patients. Tomlins et al. [71] classified patient expression profiles into subtypes in order to characterize the clinical and molecular characteristics of those subtypes. Researchers found through multivariate analysis that m-ERG + tumors were significantly associated with lower Gleason score, lower PSA, and European American ethnicity. m-ETS+ prostate cancer was significantly associated with increased seminal vesicle invasion, and m-SPINK1+ tumors, molecularly similar to triple negative prostate cancer, were overexpressed in African Americans.

A 17-gene RT-PCR diagnostic assay that yields a Genomic Prostate Score (GPS) has been clinically validated to predict biochemical recurrence, adverse pathology and metastasis in men with low and intermediate risk prostate cancers [72]. The GPS assay and other commercially available genomic tests provide additional support for treatment recommendation in the management of prostate cancer.

Conclusion

$11.85 billion was spent on prostate cancer care in the U.S. in 2010 [73]. The pervasiveness of prostate cancer and the harmful consequences of the current standard of care have led to unnecessary deterioration of quality of life and rampant costs of treatment. The uncertainty in distinguishing between aggressive and indolent lesions has warranted the improvement of imaging techniques, genetic biomarkers, and targeted therapies in order to more appropriately treat individual cancers. More long-term data are needed in order to determine the effectiveness of targeted therapies, and a larger volume of patient expression profiles must be classified as the transition away from generalized screening towards more precise genomic testing is completed.

Acknowledgment

This work was drafted as part of the University of Colorado Cancer Research Summer Fellowship, supported by the University of Colorado Cancer Center and the Cancer League of Colorado. I would like to thank my preceptor Dr. Al Barqawi for providing insight and guidance in writing this paper.

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