
The Mind

Focal Cryotherapy in Low-Risk Prostate Cancer: Are We Treating the Cancer or the Mind?

Leonardo de Oliveira Reis^{1,2,3}, H. Ballentine Carter¹

¹Department of Urology, Johns Hopkins Hospital, Baltimore, MD, USA; ²Professor of Urology, Faculty of Medicine (Urology) Center for Life Sciences, Pontifical Catholic University of Campinas (PUC-Campinas) Campinas, SP, Brazil; ³Department of Surgery, Division of Urology, School of Medical Sciences, University of Campinas, UNICAMP, Campinas, SP, Brazil

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INTRODUCTION

Since the late 1980s, the widespread use of PSA for opportunistic prostate cancer screening allowed treatment at an earlier stage, and at least in part, was responsible for a 30-40% decline in prostate cancer mortality (1). However, the stage migration favoring early localized disease, inevitably also brought the downstream effects of a diagnosis, including the enthusiasm for aggressive treatment of virtually all men who are diagnosed, driven by a myriad of forces: - inability to precisely determine the long-term risk of harm without treatment, - factors other than disease characteristics such as the limitation of using evidence to inform practice (2), and perverse incentives that often drive physician recommendations (3), commensurate with the adoption of robot-assisted laparoscopic radical prostatectomy (4, 5).

Consequently, considering the relatively high prevalence and ease of detecting, mainly low-risk cancers (6), the benefits of PSA introduction to clinical practice came with the substantial cost of over diagnosis and over treatment of many men, raising the question of whether PSA screening is associated with more harm than benefit (7).

Considering the lead-time of 6-12 years afforded with PSA testing and the generally long natural history of prostate cancer (8), high-level evidence supports the low risk of harm without treatment from favorable-risk prostate cancer in older men.

In fact, while an estimate of number needed to screen (NNS) or number need to treat (NNT) at a single point in time can be misleading, and also sensitive to comorbidity status at baseline, using a bootstrap approach the 95% CIs for NNS can be as wide as 323 to 1052 and NNT 11 to 35 to prevent one prostate cancer death at >10 years (9).

In the PSA era, Parker et al. (10) estimated the 15-year risk of prostate cancer mortality to be 0-2%, for men aged 55-74 years diagnosed with a Gleason score of ≤ 6 and managed conservatively, such as due to considerable lead time, curative intervention is unlikely to improve health for those with a <20 year life expectancy.

Even for those patients that to a large extent would not be considered favorable risk by today's classification schemes and did not have screen-detected prostate cancers, when aged ≥ 65 years, no overall, cancer-specific, or metastatic-free survival benefit was associated with surgical treatment when compared with no treatment at 12 years, suggesting the probable absence of a cancer-specific survival benefit well beyond 12 years in The Scandinavian Prostate Cancer Group Study 4 (SPCG-4) (11).

Trying to minimize the impact of over diagnosis, a consensus conference also recommended “consideration be given to changing the term used to describe low-grade prostate cancer to one other than cancer” (12). The problem is that the cancer grade, which is the strongest predictor of cancer-specific mortality with or without treatment of prostate cancer, can be misclassified in as high as almost half of cases when evaluating 12 core biopsies and radical prostatectomy specimens (13).

Then, a primary concern with a surveillance option is the underestimation of cancer grade on a prostate biopsy that could potentially compromise long-term cancer control. This uncertainty drives many physicians to recommend curative intervention fearing the real chances of risk underestimation, generating wide variations in practice patterns of management for favorable-risk prostate cancer (5).

In this regard, in an attempt to limit the uncertainty regarding the long-term risk of a prostate cancer that is found to be of low grade on a prostate biopsy, subclassification of men as very-low-risk disease is associated with a lower likelihood of adverse features at the time of radical prostatectomy, and biochemical recurrence after treatment (14, 15), when compared with those with low-risk disease. However, this strategy denies the benefits of active surveillance to many men with indolent disease who do not fit the more stringent criteria.

An additional sensitive point is the unanswered question about the extent, if any, to which a man on surveillance who undergoes delayed intervention risks losing the opportunity for control of disease (5). However, it could be argued that deaths occur in men who had advanced disease to begin with, and that surveillance usually does not compromise length of life (16).

While the 15-year risk of death from another cause for a man age 65 years would be $\approx 40\%$ (17), a man with a very-low-risk prostate cancer entering an active surveillance program who chose surgery if biopsy re-classification occurred, would have over a 10-year period, a 10% risk of having a Gleason score 3 + 4 on surgical pathology and a 15-year risk of a prostate cancer death of $< 1\%$ postoperatively; and over 10 years a 13% risk of a Gleason score 4 + 3 on surgical pathology, and a 15-year risk postoperatively of a prostate cancer death of $\approx 1\%$ (5). It was estimated that as compared to active surveillance for favorable risk prostate cancer, the average projected increase in life expectancy with immediate radical prostatectomy was 1.8 months (18). In the end, death in men on active surveillance occurs most commonly from cardiovascular disease, and death from prostate cancer is rare.

In terms of quality of life of men age 65 years managed with surveillance and curative intervention, active surveillance was associated with the longest quality-adjusted life expectancy (QALE) and surgery the shortest, but the results were highly dependent on a man's preferences with respect to living with cancer and having it treated (19).

In other words, under the most optimistic assumptions regarding postsurgical erectile dysfunction and incontinence, a man age 67 years in average health with low-risk prostate cancer, would experience ≈ 10 years of side effects for each additional year of life gained (20).

In support of exploring patient preferences for living with cancer and side effects of treatment as part of shared decision making, while definitive treatment brings a low probability of adding years to life in the low risk scenario, management options with lower side-effect profiles (e.g. focal therapy) might be associated with a lower cost in a broad perspective.

The enormous disparity between the prevalence of histological prostate cancer and the lifetime risk of mortality from prostate cancer ($\approx 2\%$) emphasizes that most low-risk patients should not be treated at all. However, the burden of active surveillance, related to its psychological impact, repeated biopsies and associated morbidities, cost and risk of missing the treatment window, needs management.

TREATING MINDS?

It is well accepted that given the alarmingly high rates of over treatment for prostate cancer (11), any man with favorable risk prostate cancer should understand that without treatment, harm from disease is unlikely in the first decade. However, progression of disease could occur in some men resulting in harm without treatment in the second decade after diagnosis and beyond (5).

In this context, the impact of living with “untreated” cancer must be considered when deciding whether to undergo active surveillance; patients and clinicians must weigh the psychological burden of living with prostate cancer and manage the uncertainty associated with gaps in the published literature.

Although one must acknowledge that those patients choosing surveillance may have made this decision because they experienced low anxiety and distress and are psychologically prepared in advance, the surveillance process can also impose a burden (21). For example, events such as a screening visit or follow-up PSA measurement evoke an increase in concern that decreased significantly after a normal result (22).

Suggesting an additional psychological burden in terms of anxiety over the uncertainty of the future or fear of losing the opportunity for a cure as important drivers of treatment (23), up to 18% of patients initially under active surveillance for very-low-risk prostate cancer might be over-treated with no evidence of progression (24).

Supporting the hypothesis that even very-low-risk prostate cancer when untreated undermines psychosocial domains, we recently showed that when focal cryoablation, brachytherapy and active surveillance are offered in an equal access protocol, those choosing surveillance were older, presented higher hopelessness (BHS) and lower general health perceptions (SF-36) scores than patients opting for focal cryoablation and brachytherapy, $p=0.0014$, $p=0.0268$ and $p=0.0168$, respectively. Patients on brachytherapy had higher IPSS scores compared to those under focal cryoablation and surveillance, $p=0.0223$. For all included patients Spearman correlation (r_s) was very strong between BHS and general health perceptions ($r_s=-0.800$, $p<0.0001$), and weak/moderate between age and BHS ($r_s=0.405$, $p=0.026$) and between age and general health perceptions ($r_s=-0.564$, $p=0.001$) (25).

In an attempt to avoid living with “untreated” cancer, and filling the gap between surveillance and radical definitive treatment (radical prostatectomy and external radiation), focal therapy might in some circumstances represent the halfway between the hypothetical under-treatment and over-treatment (25).

As decisions about treatment receipt are unquestionably influenced by cancer related fear (26), men should be provided with more psychosocial support to perhaps delay treatment and the ensuing decrements in health related quality of life (HRQoL). In such a scenario, psychological support may be indicated during active surveillance in a selected group of patients (27), and eventually a focal therapy offered to avoid unnecessary radical treatment.

One should consider that patients might leave active surveillance prostate cancer programs motivated by their own personal criteria for seeking treatment, which may differ from formal clinical or physician criteria (23). Thus, we believe that there is a need to re-examine the psychological distress and the directed support patients under active surveillance are getting.

FOCAL THERAPY

Both active surveillance and focal therapy are based on the rationale that tissue preservation is important when it is possible, however focal therapy adds morbidity to surveillance.

While most low-risk tumors do not need treatment, for those cases that need treatment after re-classification, a nerve-sparing radical prostatectomy may be the most rational option for the youngest and healthiest patients.

Considering the relatively short follow up of focal therapy cohorts, recent evidence suggests that focal treatment can rescue some patients that are uncomfortable with the concept of “untreated” cancer, thus avoiding unnecessary radical treatment (treating their minds). However, a strategy of adding focal therapy to active surveillance to broaden the group of men that will be able to adopt a tissue preserving strategy is yet to be proven in terms of oncological safety in avoiding radical therapy at the whole-gland level (28).

Uncertainty that remains relates to the durability of outcomes over the longer term and the comparative effectiveness of focal therapy as compared to other treatments. In the future, improvements in diagnostic precision (shared by active surveillance strategy), and also in ablation precision are needed for focal treatment advancements (28).

FUTURE

The USPSTF advocates against PSA screening because risks likely outweigh benefits (7). However, to avoid a return to the pre-PSA era when men with prostate cancer typically presented with advanced incurable disease, an alternative solution would be to treat selectively after diagnosis, offering treatment based on the patient’s disease characteristics, co-morbidity risks, and personal preferences. This would likely result in a decrease in the NNT for each death avoided (29), eventually leading to a re-consideration of acceptance of the value of prostate cancer screening.

While we await improved markers of an indolent and lethal phenotype, and better imaging to monitor favorable-risk disease (30), active surveillance is an underutilized management approach that could reduce overtreatment (31). Focal therapy might be considered an important theoretical part of an active surveillance program as a tissue-sparing alternative for men that wish treatment for a favorable risk cancer.

Before acceptance of focal treatment as an oncologically effective approach, there are important unanswered questions: Can focal treatment really alleviate the psychological burden of men unable to live with “untreated” cancer with acceptably low morbidity, avoiding unnecessary radical treatment? Is focal therapy an alternative to active surveillance that could reduce cost and morbidity and thus be of higher value as compared to surveillance?

CONCLUSION

The standard of care for most men with screen detected low-risk prostate cancer in most evidence-based guidelines is active surveillance. Focal therapy, which is not yet an accepted treatment in any guideline, may complement active surveillance for those men that do not tolerate living with “untreated” cancer, further minimizing the overtreatment rates. In the last scenario, there is no evidence to support that focal treatment is acting beyond patients’ minds.

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*Leonardo O. Reis, MD, PhD
and H. Ballentine Carter, MD
Department of Urology
Marburg 145, Johns Hopkins Hospital
600 N. Wolfe
Baltimore, MD, 21287-2101, USA
E-mail: reisleo.l@gmail.com*