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When “Dueling Technologies” are Mistaken for Progress

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Prostate cancer is increasingly being diagnosed at an early stage. Because these tumors are organ-confined, they have a favorable prognosis and an expected long survival, often without therapy. Despite data (1) suggesting overtreatment of newly diagnosed patients, the majority of patients will receive definitive treatment, with only 8.2% electing deferred treatment, according to a recent US survey.(2) The need to produce a safe, effective, and easily applied method to treat these cancers has prompted both academia and industry to respond with new technologies in a duel to claim progress in treatment. It is no surprise then that a proliferation of refinements in surgery and radiation and new technologies to deliver alternative energy sources have been applied to control favorable-risk prostate cancer. However, many of these approaches are applied clinically with little formal evidence to support their relative efficacy and toxicity claims.

The reasons for the lack of robust evaluation of these new technologies are valid. Studies to demonstrate improved efficacy are lengthy and costly. Given the favorable prognosis of patients in this category, efficacy often cannot be determined for many years if ever. The proliferation of these methods—and the claims of efficacy and reduced morbidity—are creating confusion in the health care community and among patients. The landscape of therapy for men with low-risk prostate cancer has become a contest among costly, competing technologies without supporting rationale.

These technologies require a framework to test their validity (Figure 1). Central to this framework is acceptance of the principle of “incremental gain.” Although the principle may appear self-evident, the allure of new technology has proved difficult to resist. As a consequence, “feasibility” with limited evidence of safety and efficacy has often been regarded as sufficient for clinical application. A framework to guide development and establish criteria for the acceptance of new technologies is required to establish order from chaos. Three broad criteria must be considered in this framework: (1) improved efficacy, (2) improved morbidity profile (complications), and (3) broader health care considerations such as ease of application, training, and cost. It is beyond the scope of this Commentary to comprehensively review data or to make comparisons among the many new technologies. I provide here selected examples of technologies that have achieved a level of clinical application in localized prostate cancer. My goal is to illustrate how the information promoted by these technologies is insufficient for physicians and patients to make knowledgeable decisions about care. It is my hope that the resulting discussion will prompt the development of an efficient and methodical approach to the application of new technologies in prostate cancer therapy.

Incremental Efficacy

Perhaps the most challenging of these criteria is incremental efficacy. If efficiency of therapeutic development is a goal, efficacy criteria cannot be driven by follow-up and long-term survival. Current treatment of early disease—even early metastatic disease—takes an extraordinarily long time to demonstrate a difference in survival. The efficient development of new interventions based on claims of retained or improved efficacy will depend on surrogate markers. Until surrogates are accepted, applying new technology to therapy for favorable-risk prostate cancer will be difficult. Review of available data is itself a reflection

of the difficulty. Surprisingly, there are no studies that can be used to compare survival or progression-free survival rates in the commonly used new approaches. It logically follows that recommendations to apply these approaches outside the context of a clinical trial are not evidence-based.

Improved Morbidity Profile

Concerns that add to the controversy around screening and early detection can be attributed to patients' fears of complications, such as incontinence and impotence. Despite significant improvements in radiation therapy and surgery, incontinence and impotence remain major concerns for patients and their physicians. The rates of incontinence attributed to prostatectomy have progressively reduced in contemporary surgical series, as have the complications of radiation therapy by improved targeting. However, erectile dysfunction remains a significant side effect, and the majority of patients experience a decline in potency or impotence.⁽³⁾ A meaningful reduction in the frequency and degree of erectile dysfunction would be a significant improvement in quality of life.

In most reports to date, complication rates and severity are not collected by validated instruments in adequately powered studies to allow us confidence in the conclusions. Planning prospective studies to determine if meaningful reduction in toxicity can be achieved by application of new technologies is difficult but necessary.

Clinical Trials

Clinical studies designed to determine the effects of the new intervention in each of the domains of study will need to be developed and applied. Overall survival and symptom-free or cancer-free survival are well established criteria, and the tools to quantify complications are available. Cost and efficiency of interventions can be measured. However, investigators urgently need agreed upon common benchmarks in each domain to plan approval strategies.

Health Care Considerations

Prostate cancer is the most frequently occurring cancer in men, with an anticipated increased incidence as the world's population ages. A low cost, widely applicable method for the treatment of localized low-risk prostate cancer with reduced morbidity would transform our approach to prostate cancer treatment. Given the overlapping morbidity profiles, and the favorable outcomes reported in selected patients, the ease of application and financial considerations will likely influence the acceptance of therapy. The potential to divert increasingly scarce health care resources to unproven treatments of localized prostate cancer has generated a public dialogue. At the heart of the problem is the lack of an efficient strategy to progress from concept and feasibility studies to evidence of benefit (incremental gain). Efforts to date show little evidence of strategic planning that will lead to the efficient determination of benefit.

Conclusion

For patients to benefit from the remarkable potential of the integration of imaging and ability to safely deliver controlled energy to tissue, a framework for its application will be required. To achieve this goal, industry, patients, and regulatory experts must form an alliance. The purpose of which will be to champion the application of technology with appropriate guidelines to ensure the safest and most effective therapies are developed efficiently.

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Algorithm for Validation of Therapeutic Technology: Favorable-Risk Prostate Cancer

Figure 1.
Establishes a framework to guide investigators through initial development and feasibility testing with specific milestones for each category. Critical to success is establishing by criteria and stage of therapy development the pragmatic milestones that ensure patient safety. This framework will reduce risk to investigators by increasing the prospect that efforts at each stage of development are proportional to gain.

Table 1

Status of knowledge: Clinically applied technologies to treat favorable-risk prostate cancer

Energy Source/Technology	Treatment		Reported Studies	
	Primary	Salvage	Comparative (Efficacy)	Impact on Survival
Radiofrequency ablation	Yes	Yes	...	n/a
Cryoablation	Yes	Yes	No	n/a
High-intensity focused ultrasound	Yes	Yes	No	n/a
Proton therapy	Yes	No	Limited	n/a
Robotic prostatectomy	Yes	Yes	Limited	n/a