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TOPIC PAPER

The 'C' Words: parallels and analogies between Prostate Cancer and Covid-19

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Prostate cancer and COVID-19 share many characteristics. Both are common conditions with a heterogeneous natural history. The impact on health is widely variable. For both, the unwanted effects of the response to the disease may outweigh the impact of the disease. For both, fear of 'the C word' (Cancer/COVID) can drive overly aggressive interventions. Insights into the management of prostate cancer over the last 20 years are directly relevant to a rational approach to COVID.

Between the introduction of PSA around 1990, and 2010, more than 90% of newly diagnosed patients were treated radically [1]. The lifetime risk of diagnosis during this period increased to 18%, while the risk of prostate cancer death was less than 3%. Contemporaneously, a growing awareness emerged that over-diagnosis and overtreatment of cancer was a significant problem [2]. Nonetheless, driven largely by the legitimate goal of reducing cancer mortality, aggressive treatment remained the norm.

The concept of active surveillance, introduced by one of the authors and colleagues in 2002, [3] sought a middle ground between radical treatment for all and no treatment, by monitoring low-risk cancer for evidence of progression and treating selectively. This concept, which was extremely controversial and largely rejected initially, eventually gained wide acceptance. It has become the standard of care for most patients with low-risk prostate cancer, reflected in many national guidelines.

Covid-19 has many parallels to this trajectory. Many patients are diagnosed in whom the disease is, like Grade group 1 (Gleason 6) prostate cancer, 'clinically insignificant'. Many are asymptomatic, and others experience a flu-like illness which resolves quickly. A small fraction suffer serious illness, and a smaller fraction die. A recent overview of 61 COVID population studies estimated the infection fatality rate from 0 to 1.5%. [4]. The median rate in the studies was 0.23%. In individuals < 70 years of age, the range was from 0 to 0.31% with a corrected median of 0.05%.

These rates are quite similar to the estimated prostate cancer mortality in low-risk prostate cancer managed with active surveillance [5]. The extensive societal 'lockdown' adopted by many countries over the last 6 months is analogous to the 'radical treatment for all' approach to low-risk prostate cancer in the pre-surveillance era.

For low-risk prostate cancer, the effect is men rendered incontinent and with erectile dysfunction for a clinically insignificant disease. With Covid, it is economic catastrophe, as well as the many adverse personal and social consequences of lockdown.

Both diseases require involve uncomfortable tests (biopsy, nasopharyngeal swabs), with well-established risks of false positive and negative tests associated with adverse health consequences.

Early stories from Wuhan, Italy and New York about ICUs being overwhelmed, insufficient ventilators to manage the surge, and sick patients unable to receive life-saving care, received global attention. This created widespread concern and panic. Like receiving a cancer diagnosis, the understandable instinct was to do whatever was required to prevent this, despite the economic and social consequences of lockdown.

Risk stratification is relevant to both diseases. In most constituencies, ICUs are not overwhelmed; most patients are asymptomatic or recovery quickly; and young patients are at extremely low risk of mortality. Elderly and infirm patients are at higher risk for Covid-related morbidity and mortality and must be protected. The analogy is to patients who are diagnosed with high risk localized or metastatic prostate cancer. Individuals who live with or in close contact with these patients may acquire infection and are analogous

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to intermediate risk localized prostate cancer, whose risk of mortality is low but not negligible. The majority of the population, based on age and health, are deemed low risk. The tiny minority of the young and healthy who are seriously affected are comparable to the 25% of low-risk prostate cancer patients who harbor occult higher grade disease. These patients, when identified, are treated definitively, with a favorable outcome in most cases, but about 1% will develop metastases. As with prostate cancer, where ancillary diagnostic biomarkers and imaging evolved for better risk stratification, we expect Covid-specific ancillary tests and technology (e.g. serology, viral load tests, etc.) to evolve and improve risk assessment and prognostication and guide treatments.

With both diseases, most patients dying are elderly, and the number of QALYs saved by aggressive management for all is modest.

When the active surveillance concept was first promulgated, almost 20 years ago, it met a firestorm of criticism. Proponents (like the author) were warned, 'Men will die unnecessary deaths, and you will be responsible'. Conservative management was deemed unethical in men with curable disease. It took the cumulative experience of many prospective surveillance cohorts showing very favorable outcomes, and the USPSTF decision in 2011 against PSA testing based on over-diagnosis and overtreatment to overcome these objections.

Similarly, many experts promulgated terrifying predictions of the pandemic. In March 2020, the Imperial College COVID-19 Response Team published an official and widely disseminated report estimating that 81% of Americans would be infected and 2.2 million Americans would die [6]. The actual number of COVID deaths in the US by the end of Sept 2020 was 192,000. It is plausible that many of these deaths were COVID unrelated, in people who had tested positive but had competing causes of mortality. This level of mortality is high, and tragic, but less than 10% of what was predicted by this expert panel. These predictions were fear mongering.

Those counseling moderation of highly restrictive COVID prevention policies is criticized as being irresponsible, insensitive, and lacking in compassion. Individuals who fail to adhere strictly to social distancing or mask wearing are condemned, fined, and in some cases subject to violence.

Active surveillance of GG1 prostate cancer does not mean absence of intervention, just as the alternative to massive lockdown is not a free for all. Patients require long-term follow-up, serial PSA and imaging, and biopsy. Similarly, common sense policies should be applied to COVID. Increasingly, experts are acknowledging this. The recent 'Great Barrington Statement' concludes 'Those who are not vulnerable should immediately be allowed to resume life as normal' [7]. Efforts should be invested in the development and rapid integration of better tools that can identify patients at risk. Patients at risk (elderly and the co-morbid) should be protected vigorously. We did it for prostate cancer and we can do it for COVID.

COVID is likely here to stay. Vaccines have been developed in record time, but there are significant questions about effectiveness, long-term safety, and access. The capacity for adaptation is our greatest characteristic as humans. We must adopt the principles of active surveillance—risk stratification, a realistic assessment of the threat without fear-mongering, matching of the severity of the disease to the aggressiveness of the treatment/degree of economic and social restriction, continuing re-assessment of risk, and a return to normal life as much and as quickly as possible.

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