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TOPIC PAPER

Overdiagnosis in urologic cancer

For World Journal of Urology Symposium on active surveillance in prostate and renal cancer

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Abstract

Background Cancer, which historically was diagnosed at late and incurable stages, has expanded to a heterogeneous group of conditions that vary from clinically insignificant to rapidly aggressive and lethal. This evolution is due to the widespread use of screening tests for early detection of cancer, both directed (i.e., PSA, mammography, colonoscopy) and undirected (abdominal imaging). The use of these tests has resulted in both benefits and harms. The benefits are a reduction in survival and mortality, due to significant cancers being diagnosed at a more curable stage. The harms are an increase, in some cases dramatic, in the diagnosis of clinically insignificant disease. These are called 'cancer' but not destined to affect the patient's life, even in the absence of treatment.

Methods Non-explicit summary of the literature on overdiagnosis of cancer.

Results The phenomenon of overdiagnosis requires two factors: the presence of a common reservoir of microfocal disease and a screening test to find it. These factors exist for breast, prostate, skin, renal, and thyroid cancers, and to a lesser degree for lung cancer. The problem of cancer overdiagnosis and overtreatment is complex, with numerous etiologies and many tradeoffs. It is a particular problem in prostate cancer but is a major issue in many other cancer sites. Screening for prostate cancer based on the best data from prospective randomized trials significantly reduces cancer mortality. However, reducing overtreatment in patients diagnosed with indolent disease is critical to the success of screening.

Conclusion Active surveillance, the focus of this series of articles, is an important strategy to reduce overtreatment. This article reviews the pathological, clinical, social, and psychological aspects of overdiagnosis in cancer.

Keywords Prostate cancer · overdiagnosis · overtreatment · active surveillance · screening

Background

Cancer evokes fear. Humanity's relationship with cancer is ancient, being first recognized as a distinct entity by Egyptians. Until the modern era, cancers were diagnosed late and usually at an incurable stage. This view, of cancer as a uniformly lethal disease, is still quite widespread. Dorland's medical dictionary in 1996 defined cancer as 'a neoplastic disease the natural course of which is fatal' [1].

At the website 'Dictionary.com' [2], cancer is defined as 'a malignant and invasive growth or tumor… tending to recur after excision and to metastasize to other sites; any evil condition or thing that spreads destructively'. Malignant is defined as 'having the properties of anaplasia, invasiveness, and metastasis; said of tumors tending to become progressively worse and to result in death' So whether it is 1900, 1994, or 2020, being diagnosed with 'cancer' portends a poor outcome and death. Neither definition provides much solace to the newly diagnosed.

These definitions used to be appropriate. In the era prior to widespread imaging and testing, patients were diagnosed after they became symptomatic. Those symptoms usually occurred late in the course of the disease. In most cases patients presented with hematuria and flank mass from advanced kidney cancer, bone pain from metastatic prostate or breast cancer, hemoptysis from advanced lung cancer, or bowel obstruction from advanced colon cancer. These patients usually had a short, miserable life after diagnosis.

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Indeed, one of the first observations of clinical epidemiology in oncology was a seminal paper showing that the survival of patients with colon and lung cancer was predicted more by whether they were diagnosed on the basis of symptoms (unfavorable), vs serendipitously after a diagnostic test (favorable), than by grade or stage [3].

The epidemiology of cancer changed dramatically with the advent and widespread implementation of new diagnostic tests, including PSA, mammography, abdominal ultrasound, and colonoscopy. These tests advanced the time of diagnosis and decreased the volume and stage at which cancers are detected. This is 'stage migration'. Cancers are now commonly diagnosed well before they would be expected to produce symptoms or manifest signs. This 'lead time' is often many years. Some diagnosed cancers would never be found, and pose no threat to the life of the patient. This results in 'overdiagnosis', a term that is still not defined in Dorland's Medical Dictionary!

The word 'cancer' includes a wide range of conditions. At the minimum, a 'cancer' is a group of cells that look abnormal. Histologic assessment has a great deal of prognostic power, but the natural history of cells which may look identical is variable. Some are very indolent, and grow slowly, if at all. Some may regress spontaneously. Others grow very quickly, metastasize early, and are rapidly lethal. 'Cancer' is a pathological description of tissue made at a single point of time. It is not, in and of itself, a prognostication about the natural history of the disease.

However, in the public mind, as in Dorland's dictionary, cancer is still a lethal disease to be destroyed, irrespective of cost and quality of life effects. This reaction can lead to overtreatment, with very significant side effects and costs. These side effects can be lifelong. While that may be warranted and readily justifiable for a life threatening disease, it is nothing short of a tragedy when these are incurred for an insignificant entity.

The problem of cancer overdiagnosis

This describes a cancer that is diagnosed (usually by a screening test) that would not otherwise result in symptoms or death. Overdiagnosis occurs when the cancer is destined not progress, or because the rate of progression is so slow that the patient dies of other causes before it produces symptoms or signs. This second feature incorporates three factors: the rate of growth, the volume of cancer at the time of diagnosis, and the patient's co-morbidity and life expectancy due to age and competing mortality risks. In a patient with a limited life expectancy, a cancer that grows rapidly may still be overdiagnosed. A key point is that, a cancer that is overdiagnosed has all the pathological characteristics of cancer. It is quite different from, a 'false positive' diagnosis (i.e., where a disease is falsely identified).

Cancer is a complex disease involving many aberrant genetic pathways. Because these alterations are so variable, cancer progression is unpredictable. Some genuine histologic cancers may never grow, or spontaneously involute [4]. Spontaneous regression of small cancers is likely more prevalent than is appreciated. Lack of VEGF may result in inability to induced neovascularity, thus dooming the cells to outgrow their blood supply [5]. Lack of telomerase may result in intrinsic cell senescence [6]. Host immunity may induce cancer death. A lot of spontaneous regression likely occurs at a subclinical level, involving cancers in the millimeter range, and therefore unnoticed by patient or physician.

Other cancers may grow so slowly that the patient will die of another cause before it causes symptoms. A 3rd group progresses slowly, and may lead to symptoms and death, but only after many years. Only the fourth group represents the classic cancer phenotype, i.e., a fast growing, lethal cancer resulting in death months or a few years after diagnosis. These represent the minority of cancers diagnosed in the modern era.

Non-progressive or very slow growing cancers that develop in the majority of healthy men as they age can be termed 'pseudo-diseases'. Most pose no direct threat to the patient. They can pose indirect threats, including the anxiety and other psychological effects associated with the cancer diagnosis, and the risks associated with (unnecessary) treatment.

The conundrum is that it can be difficult to determine with confidence when a cancer diagnosis is an overdiagnosis. Overdiagnosis can only be ascertained with certainty when the patient, untreated, dies of other causes. Because one can't know this outcome with 100% confidence at diagnosis, a common response is to treat all such patients. This results in considerable costs, both financially and quality of life related. While treatment in these patients provides no benefit, it carries the risk of potentially serious adverse effects. However, an understanding of the natural history of these diseases, and the ability to stratify for risk using clinical parameters, means that overtreatment can be substantially reduced. Figure 1 illustrates the magnitude of the problem of overdiagnosis, resulting in the potential of large numbers of people being labelled 'at risk', including many not destined to develop life-threatening disease [7].

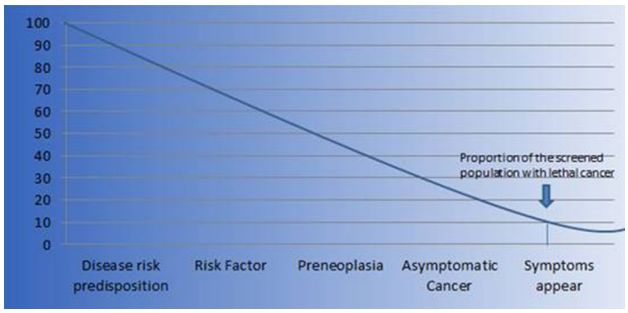

Fig. 1 **a** This illustrates the difference between a true epidemic of serious disease, where a rise in incidence is paralleled by an increase in mortality, and a 'pseudo-epidemic', or overdiagnosis, where the rise in incidence is not mirrored by an increase in mortality. **b** Rate of new diagnoses and death in five cancers in the Surveillance, Epidemiology, and End Results data from 1975 to 2005 [12]. For these cancers, over 30 years between 1975 and 2005. A significant increase in age adjusted incidence was observed, without a corresponding increase in mortality. This may reflect overdiagnosis and/or improved treatment

Requirements for overdiagnosis

Prevalence of microfocal disease

Autopsy series have shown for many years that microscopic cancers are common in people dying of unrelated causes. Prostate, breast, and thyroid cancer in particular have been identified in autopsy series, partly because these organs are small enough to permit serial sectioning of the entire organ.

Sakr reported on the analysis of 525 men dying of trauma [8]. Remarkably, 30% of men in their 30 s were found to have prostate cancer. This increased linearly with age. In fact, at any age, the likelihood of harboring prostate cancer was equivalent to the patient's age as a percent (i.e., 80% of 80 year olds). This was independent of race. Similar results, confirming the high prevalence of microfocal prostate cancer at autopsy have been reported by others [9, 10]. In one landmark study, 36% of autopsies revealed some prostate cancer. Average tumor volume was 0.303 cm^3, and in those with cancer GS 7 or greater was present in 23% of Caucasians and 51% of Asians [11].

Systematic examination of the thyroid at 2.5 mm intervals identified papillary carcinoma in 36% of adults in Finland. These were smaller than the slice thickness, and the authors concluded that serial sectioning would identify these lesions in close to 100% of human beings [12].

Four autopsy series which report age related prevalence of breast cancer indicate that 7–39% of middle aged women harbor microfocal breast cancers. This is a wide range. It may reflect differences in pathologists' willingness to call a very small lesion cancer, or rigorousness of analysis of all tissue. Slice number ranged from 10 to 200 in these studies [13].

For these cancers, the likelihood of harboring foci of cancer is dramatically higher than the lifetime risk of dying of disease. Were the entire reservoir of disease detected, the probability of overdiagnosis would be about 90% for prostate, 45–90% for breast, and 99.8% for thyroid [14].

Disease detection

Efforts at detection are required to identify this large reservoir of microscopic cancer. The second condition is therefore an early cancer detection test.

Cancer screening refers to efforts to detect cancer in asymptomatic patients. This includes examining patients for moles or lymphadenopathy at the time of a periodic health exam, as well as PSA, mammography, or colonoscopy.

Tests unrelated to screening can also result in early cancer detection. The advent of widespread diagnostic imaging to evaluate symptoms not suggestive of cancer often leads, serendipitously, to an early cancer diagnosis. Scans of brain, chest, abdomen, and pelvis often show abnormalities suggestive of cancer. Further, as ultrasound, CT, and MRI have become more sensitive, the lesions are detected at an earlier and earlier stage. Approximately 85% of asymptomatic middle aged patients have some abnormality identified on CT of the abdomen. The use of abdominal imaging has increased dramatically over the last 20 years [15].

Surgical procedures for benign conditions, i.e., TURP, may result in cancer detection [16]. An additional factor is the increased sensitivity of diagnostic tests. In the case of prostate cancer, this includes both a steady decrease in the PSA threshold considered abnormal, and an increase in the number of cores taken. The emergence of prostate MRI early in the diagnostic algorithm of prostate cancer also poses a risk of identifying many indolent cancers, although targeted biopsies are less likely to find low grade prostate cancer than systematic biopsies.

Evidence that early detection has led to overdiagnosis

The most powerful evidence for overdiagnosis comes from randomized screening studies. Screening results in an increase in number of diagnosed cases, due to early detection. If all of these cases were clinically significant, the number of cases in the control group would 'catch up' during long term follow up, as clinical disease manifested itself by symptoms (or death). A persistent gap in case number

Table 1 A summary of the estimated rate of overdiagnosis of common cancers

Cancer type	Estimated amount of overdiagnosis	Screening modality
Prostate	50–60% [19]	PSA
Kidney	Twofold increase in incidence but no increase in deaths [19]	Incidental detection on abdominal CT
Breast	25% [19]	Mammography
Lung	13–25% [20]	CT
Thyroid	Twofold increase in incidence but no increase in deaths [22]	Incidental detection by imaging performed for other reasons, i.e., sinus symptoms, headaches or neck palpitation
Melanoma	Approximately 50–60% [21]	Crude estimate based on population trend

between the two groups suggests that overdiagnosis has occurred. In breast cancer, only one trial has reported long term follow up data on incident cancers [17]. The estimate from this study was that 24% of mammographically detected cancers were overdiagnosed. Overdiagnosis has also been demonstrated in prostate, kidney, lung, thyroid, and melanoma (Table 1) [18].

Cancer mortality has fallen 15% in the US since the mid-90 s. Approximately 600,000 fewer deaths have occurred in the last 10 years than would be expected had previous mortality trends continued. Much of this reduction is likely due to earlier detection of many cancers. About 25% of these 'avoided' deaths were due to reduction in prostate cancer mortality. Screening for prostate cancer has been associated with a 40% fall in prostate cancer mortality in the US over the last 25 years, from 38/100,000 in 1995 to 22/100,000 in 2018, according to 2020 statistics [23]. Since PSA testing was discouraged by the USPSTF recommendation in 2011, there has been a significant stage migration upwards, with an increase in the rate of metastatic prostate cancer at diagnosis. After 20 years of steady decline, prostate cancer mortality in the US has also ticked upwards in the last few years.

The PLCO screening trial [24] had a 22% increase in detection in the screened group. The ERSPC trial [25] found 34 additional cases per 1000 men in the screening arm, an increase of about 60%. Modeling studies have also suggested that the risk of PSA detected prostate cancer being 'overdiagnosed' is about 67% [26].

Observational studies in a number of tumor sites also suggest frequent overdiagnosis. Japan introduced a national screening program for neuroblastoma in infants. The number of cases in the screened group increased fivefold. Based on concerns about overdiagnosis, conservative management was recommended to diagnosed patients. 100% of the 11 cancers managed this way regressed [27]; all represent cases of overdiagnosis.

Evidence of cancer overdiagnosis is clear in population studies. In cases of a true increase in the amount of cancer, rising incidence is accompanied by rising mortality rates. In case of overdiagnosis, mortality remains stable or diminishes. An example of a true increase in both incidence and mortality is esophageal cancer [28]. Based on datasets like SEER, overdiagnosis is suggested in the cases of melanoma, thyroid, breast, prostate, and kidney cancer.

For thyroid cancer, the rate of diagnosis has doubled in the last 30 years, with no change in death rate. The increased new cases are confined to papillary thyroid cancer, which has the most favorable prognosis [29]. It is estimated that overdiagnosis in women accounts for 90% of thyroid-cancer cases in South Korea; 70–80% in the United States, Italy, France, and Australia; and 50% in Japan, the Nordic countries, and England and Scotland [30]. In Japan, thyroid-cancer incidence among screened children and adolescents was approximately 30 times as high as the national average only a few months after intensive screening programs for these age groups began in response to the 2011 nuclear accident [31]. For melanoma, the diagnosis rate has increased almost threefold, from 7.9 to 21.5 per 100,000 [32]. Most of these are localized, in situ melanomas, and their rate of diagnosis closely mirrors population skin biopsy rates.

Kidney cancer rates have doubled from 7.1 to 13.4 per 100,000, reflecting the widespread utilization of ultrasound and CT imaging. A number of recent series have confirmed the indolent behavior of many kidney cancers [33, 34]. A study of the growth rate of 53 solid renal tumors, in which each tumor had at least two CT volumetric measurements 3 months apart before nephrectomy, demonstrated their variable natural history and frequent indolence [35]. Twenty-one (40%) had a volumetric doubling time of more than 2 years and seven (14%) regressed. Furthermore, slow-growing tumors were more common in the elderly. Many renal tumors thus are overdiagnosed either because they do not grow at all or because their growth is too slow for the tumor to cause symptoms before the patient dies of other causes. In the absence of systematic screening for renal cancer, the increased rate of diagnosis is likely due to the increased use of abdominal imaging. A recent epidemiologic study showed a clear correlation between the prevalence of abdominal imaging in Medicare patients in different regions of the US, and the likelihood of treatment for kidney cancer [36].

Overdiagnosis and overtreatment of kidney cancer has multiple negative consequences, including unnecessary care,

loss of kidney function, the risk of surgical complications, psychosocial stress, financial toxicity, and the potential for worse survival due to long term effects of reduced GFR [37].

For bladder cancer there is an emerging consensus that overly intensive surveillance has led to overdiagnosis of clinically insignificant cancers, and overtreatment [38]. Active surveillance of low grade recurrent TCC has been employed successfully [39].

For both breast and prostate cancer, mortality rates have decreased despite the marked increase in diagnosis. Prostate cancer mortality in the US has fallen by about 40% since 1993, from 38.6 to 24.6 per 100,000. A similar trend has been seen in breast cancer. This decrease has multiple causes. The two most probable are the effects of early detection, and improved therapy. Thus, in these two cancers, early detection is likely producing both overdiagnosis and a mortality benefit. There is an important distinction between the effects of screening for prostate and breast cancer. Prostate cancer screening results in a dramatic reduction in patients presenting with advanced disease at diagnosis. However, with breast cancer the rate of advanced disease at diagnosis is unchanged [40]. This may reflect a profound biological difference between the two disease, whereby prostate cancer biology is 'Halstedian' and breast cancer 'Fisherian'. The Halstedian model holds that cancer arises at a single location, grows there, and eventually migrates to local lymph nodes and then to more distant organs, allowing cancers destined to metastasize to be identified at an earlier stage and reduce the incidence of cancers that first present as metastatic disease. Thus earlier detection reduces the rate of metastatic disease at diagnosis, which has been observed for prostate cancer. The Fisherian model is that microscopic metastases often develop very early in the course of disease, limiting the benefit of early detection. This dichotomy is undoubtedly overly simplified; a more likely reality is that for each type of cancer there are multiple paths to metastasis. [41] Aggressive, poorly differentiated cancers tend toward the Fisher paradigm; localized, well-differentiated cancers tend toward that of Halsted. There's evidence of such variability in both breast and prostate cancer. Nonetheless, the marked difference in stage migration between the two diseases as a result of screening is compelling.

This is a classic benefit-harm conundrum. In prostate cancer, there appears to be an undeniable benefit of early detection, reflected by a substantial and very clinically meaningful fall in mortality. This comes at the cost of many patients being treated for each one who benefits. This overtreatment problem is a major concern.

Overdiagnosis can have lifelong consequences with a false positive screening test, the adverse effects of anxiety and additional tests are short term, until the absence of cancer is confirmed. In contrast, a cancer diagnosis may influence patients' sense of well-being, their physical and emotional health, their relationship with loved ones, and their ability to purchase health insurance, even if the disease is completely indolent.

The medicalization of the healthy is another unwanted aspect of aggressive screening for early disease. 'Today the kingdom of the well is being rapidly absorbed into the kingdom of the sick, as clinicians and health services busy themselves in ushering people across this important border in ever increasing numbers' [42]. The problem of overdiagnosis is a malady of modern medicine, not just oncology. Some argue that this problem is an inevitable but somewhat unforeseen consequence of well-meaning attempts to diagnose serious diseases at a point where they are more amenable to cure; others, that it reflects vested medical and commercial interests in medicalizing the normal [43].

The risk of overdiagnosis and overtreatment makes informed decision making more complex. Early treatment may help some, but hurts others. This trade off should be calculated by each individual patient based on a sophisticated understanding of the risks and benefits involved, and insight into their own personal values and risk tolerance. The decision involves balancing many factors. This ideal is often not achieved.

Four strategies are warranted to improve this situation: (1) develop clinical and patient tools to support informed decisions about prevention, screening, biopsy, and treatment and offer treatments tailored to tumor biology; (2) focus on development and validation of markers that identify and differentiate significant- and minimal-risk cancers; (3) reduce treatment for minimal-risk disease; and; (4) identify the highest-risk patients and target preventive interventions.

Patient education is a key solution to this problem. Patients should be adequately informed of the nature and the magnitude of the trade-offs involved. This kind of discussion is challenging for patients. Scientific illiteracy and lack of numeracy contributes to the challenge [44]. (Indeed, failure of most people to understand the nature and magnitude of risk is a major social issue, and results in support for many inappropriate policies.) Patients must clearly understand the nature of the trade-off, that although early treatment may offer the opportunity to reduce the risk of cancer death, it also can lead one to be treated for a "cancer" that is not destined to cause problems. These ideas are often foreign, and must be presented clearly. The cancer 'zeitgeist' referred to earlier in this chapter, i.e., that it is uniformly a lethal and aggressive disease, contributes to the challenge.

Quantifying overdiagnosis is often challenging. There are only a few randomized trials of prostate cancer screening and even fewer provide the needed long-term follow-up data. Nonetheless, "best guess" estimates about the magnitude of overdiagnosis are useful in decision making. These estimates involve modeling the natural history of the cancer, the impact of early diagnosis, and competing mortality risks. It

isn't clear, for example, how patient preferences are influenced by whether the number needed to treat is 12 (Hugusson Scandinavian screening study) [45], or 48 (ERSPC) [25], for each prostate cancer death avoided. Simple and transparent models with explicit assumptions and input values can be instructive.

Overdiagnosis and overtreatment generates a cycle of positive feedback for more. As the disease is more widely diagnosed, more and more people have a connection to someone, whether a family member, friend, or celebrity, who "owes their life" to early cancer detection and treatment. This is the popularity paradox of screening: The more screening causes overdiagnosis, the more people feel they owe it their life and the more popular screening becomes [46]. The problem is compounded by media reports about the dramatic improvements in survival statistics, which may reflect nothing more than lead and length time effects.

Simple volume criteria can be used to identify candidates for conservative management. This is now widely accepted for small pulmonary nodules [47], renal masses (the subject of several articles in this symposium), and adrenal masses [48] detected incidentally. Identifying growth over time is another parameter that can reduce overtreatment. With lung cancer screening using CT, biopsies of small lesions are now restricted to those that grow over time [49].

The trend towards personalized medicine based on accurate prognostic and predictive biomarkers and imaging represents another powerful tool to reduce overdiagnosis and overtreatment. For example, the diagnostic paradigm for prostate cancer is shifting towards an image and biomarker based strategy. The historic approach, still widely utilized, is to use PSA, a flawed biomarker with a 60% false positive rate, to identify patients for systematic (blind) biopsy. This results in the diagnosis of clinically insignificant cancer in about 40% of newly diagnosed patients. The new strategy utilizes a second molecular serum or urine based assay to further stratify patients for their risk. These have NPVs as high as 90%. Only the patient whose molecular test is positive goes on to the next step, accurate imaging.

Multi-parametric MRI has played a major role in this area, and recent evidence suggests that PSMA imaging may have incremental value in detecting clinically significant localized prostate cancer [50]. High-resolution micro ultrasound also appears promising [51]. Imaging would be followed by a targeted biopsy, which would then be subjected to next-generation sequencing and molecular profiling driving treatment decision making. In this somewhat idealized model, almost all of the patients having a biopsy would be found to have significant disease, and almost all of those undergoing treatment will have significant cancer [52].

Another solution is to relabel the disease with a term that doesn't include words for cancer. This was done effectively for what was formerly grade 1 papillary transitional cell carcinoma of the bladder [53, 54], and is now termed PUNLMP, or papillary urothelial neoplasia of low malignant potential. It has been proposed that small volume, Gleason 6 prostate cancer be termed 'IDLE' tumors (indolent lesions of epithelial origin) [55]. This would go a long way towards reducing the problem convincing patients with a 'cancer' diagnosis to remain untreated. IDLE tumors would be managed as ASAP is currently, with serial PSA and repeat biopsy. However, most pathologists believe that, since low grade prostate cancer can demonstrate local invasion, it deserves to be labeled cancer. The grade grouping of prostate cancer is a step in this direction. Gleason 6/10, implying an intermediate grade, is now be called Group 1, reinforcing the concept of a favorable lesion [56].

Limitations of the concept

'Overdiagnosis' is defined primarily by cause of death. This means that prospective identification of overdiagnosis during a patient's lifetime is not possible. A thought experiment illustrates this. Consider the case of identical twins with underlying ischemic heart disease who are both found to have the same type of lung cancer. One is stented, and goes on to die of lung cancer. The other dies of heart disease. In the first case, the lung cancer was clinically significant; in the other, it would be considered overdiagnosis. This illustrates the limitations of the concept as pertaining to individuals, in whom death, and ascertaining its cause, is in the future. It is primarily an epidemiologic concept and, despite the limitations of identifying overdiagnosis in individuals, it can be readily identified in populations [57].

The problem of overdiagnosis and overtreatment goes beyond oncology. As physicians, we have a responsibility to recognize the phenomenon, protect our patients from it where possible, and minimize the impact in other ways. These include developing a clear definition of where it exists; describing it in simple, easily accessible terms (i.e., 'too much medicine') [58]; recognizing the competing values and risks/benefits involved, and developing strategies to account for these; and promoting public debate on the inherent uncertainties and limitations of health care and their implications for overdiagnosis.

Active surveillance, the focus of this series of articles, is a major step forward in addressing this concern, not only in prostate cancer, but in many other human conditions.

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