Prostate cancer: a systems approach overview

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Abstract

Systems thinking is a set of methodologies that facilitate analysis and predictions for a complex system in a holistic way. Prostate cancer has precursor stages that are difficult to detect and a number of different therapy options for different stages, so it is a complex disease to manage within healthcare systems. In this review we show how systems thinking, especially causal loop diagrams, can be a very valuable tool for gaining greater insight into the pathogenesis and diagnosis of prostate cancer and to predict the consequences in major changes in the pattern of healthcare for this disease, e.g. introduction of national screening programmes using serum prostate specific antigen. The systems thinking approach can be used to predict changes in histopathology workflow when other parts of the system are changed.

Keywords causal loop diagrams; influence diagrams; prostate cancer; prostate cancer screening; prostatic intra-epithelial neoplasia; prostate specific antigen; state diagrams; systems thinking

Introduction

Histopathology has an intermittent relationship with the management of many diseases because the opportunities for biopsy and histopathological examination are often limited to a few points along the disease progression. Some organs, the colorectum being an exemplar, are relatively accessible for visual inspection and biopsy so a disease such as colorectal cancer is well-represented in histopathology biopsies from early precursor lesions through to advanced disease. Other organs, including the prostate, are not available for visual inspection and the imaging and biopsy of these organs is more difficult and has less resolution than direct inspection. This leads to fewer biopsies and less participation of histopathologists in the whole spectrum of a disease. This restriction of biopsy material to a few points along the disease spectrum can lead to a distortion of histopathologists' perception of the disease and some inflexibility when faced with changes in management of that disease, e.g. introduction of a cancer screening programme.

A systems approach, often called 'systems thinking', is a methodology that sets out to create an overall model of a particular situation, which can be used to make predictions about that situation if specific elements within it are changed. The systems approach is often divided into two categories – soft and hard systems. A soft systems approach identifies all the elements within a system and the *qualitative* relationships between these. A hard systems approach goes further, taking *quantitative* data and producing a model that will produce quantitative predictions about outcomes from changes in input data. A hard systems approach will be more familiar to scientists since much translational molecular pathology research contains an element of hard systems modelling, e.g. development of a novel molecular marker that will predict systemic metastases in node negative breast cancer. The soft systems approach has had less application in the scientific and biomedical arenas and is often derided in those areas because it lacks a quantitative basis. However, soft systems methodologies have had widespread application in management 'science' where they have been shown to be very successful at addressing complex problems.[1–4] Since diagnostic histopathology is often a blend of scientific knowledge integrated within a management context, it is likely that a soft systems approach could yield valuable insights into the effects of change in the scientific knowledge or the management of diseases.

This review applies some systems approaches to prostate cancer and shows how these can focus our thoughts on the scientific facts about the disease as well as enabling us to predict how changes in management of the disease will affect histopathology services. The review starts with overly simplistic models but then builds up to more complex models that should have some clinical utility.

Phase I modelling – a simple state diagram

The simplest level of a systems approach is to identify the elements within a system without ordering them or defining any relationships between them. This may appear completely self-evident, and when one has previous knowledge of the subject it may appear unnecessary, but it is important to do this with as much inclusion as possible so that no potentially important elements are left out of the system. It becomes extremely important to do this when trying to model a new system about which there is very little initial information. If we think about prostate cancer at its most basic level we know that men are born with (we assume) normal prostates but that a sizeable proportion of men develop prostate cancer so at its very simplest level we can identify two states – normal and prostate cancer (Figure 1).

Figure 1 A simple two state representation of normality and prostate cancer.

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Of course we know that there are many more entities in the prostate cancer spectrum and so we can define those to give more elements in our state diagram (Figure 2).

This state diagram has no order to the elements, they are simply put onto the page in the order that we have thought of them, which would seem to be unhelpful but it is worth reflecting that histopathology when performed in an uncritical manner would be somewhat analogous to such a diagram. In histopathology we are taught to identify reliably discrete morphological patterns and to assign them agreed labels, which are included in our reports and should be understood by clinicians reading those reports. Diagnostic histopathology can run at this most basic level without much detriment to the overall management of patients as long as the labels can be applied to the morphological patterns with a one-to-one correspondence and a high level of reliability. However, it is much better if the elements are more ordered with clear definitions of their relationships because this gives a much greater understanding of the interaction between diagnostic histopathology and overall patient management, especially in difficult areas, e.g. atypical small acinar proliferation and early prostate cancer in needle core biopsies.

Looking at the simple state diagram in Figure 2 there are still some important points that arise. Among the entities included are neuroendocrine prostate cancer and large duct prostate cancer (shown in red in Figure 3).

When we consider those in the context of the other elements we realise that, although they are variants of prostate cancer, they are not going to fit in with the overall progression that we are going to construct. This will be based on the most common adenocarcinoma of the prostate that arises from the acini in the prostate with no special pattern of differentiation. These other entities would need to be included in a complete systems model of prostate cancer but are likely to add unnecessary complexity to our initial model so we will omit them. It also means that we need to tighten up on our terminology for the existing elements so we end the first phase of modelling with the state diagram in Figure 4.

Phase II modelling – an influence/progression diagram

Now that we have defined elements that we wish to include in the model, we can look at the relationships between these elements and indicate them on the diagram by arrows. When we look at the later stages of prostate cancer the elements are relatively easy to order. Localised prostate cancer can progress to locally advanced prostate cancer, which could, in turn, progress to metastatic prostate cancer as shown in Figure 5.

Many diagrams like this have been reproduced in the pathology literature, Walter Bodmer's progression from colorectal adenoma through to invasive colorectal carcinoma being the prototypical example. It is important to get all the details of such sequences correct as such diagrams spread rapidly through the literature, presumably owing to the much easier assimilation of information from diagrams rather than blocks of dense text. Looking at our new diagram (Figure 5) we need to look at all the elements and ensure that all appropriate arrows have been included to indicate all possible relationships. We ask ourselves whether prostate cancer can metastasise from localised, as well as locally advanced, prostate cancer. That can indeed occur so we need to draw an arrow from localised to metastatic prostate cancer, which does not pass through locally advanced prostate cancer as an obligate transitional stage (Figure 6).

We can also look at whether the arrows should be one way or two way, i.e. can locally advanced prostate cancer regress to localised or metastatic prostate cancer regress to localised prostate cancer? The answers to these questions are obviously no, at least without some very effective therapy, so the arrows should be left one way.

Including the precursor lesions to invasive prostate cancer in the influence diagram is more difficult and this is where the value of these diagrams becomes evident. Prostatic intra-epithelial neoplasia (PIN) is probably the easier of the two to deal with. What we need to know is whether PIN is a precursor from which invasive prostate cancer develops and if so is it an obligate precursor,

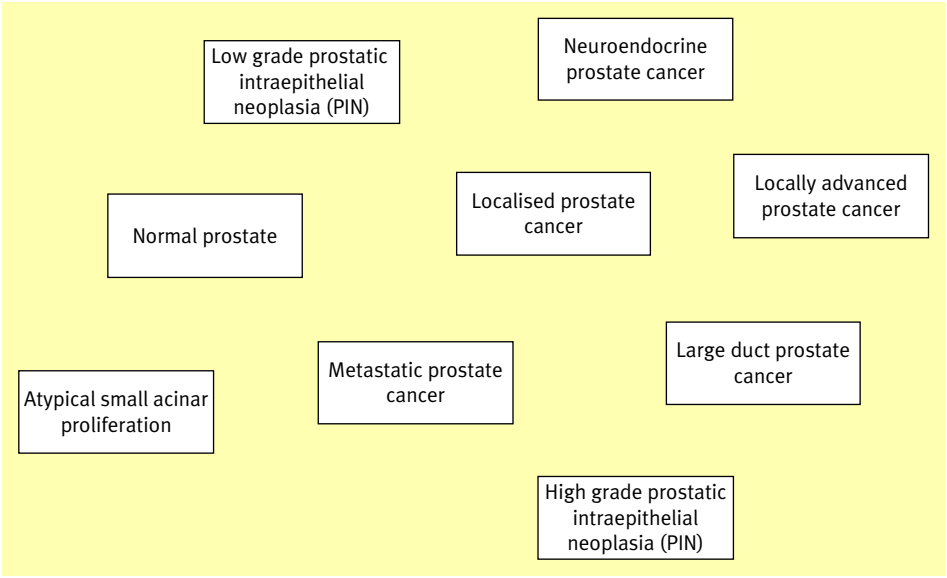

Figure 2 A state diagram showing all the elements that might be considered for a model of prostate cancer pathogenesis and progression. The elements are not ordered in any way.