

The feasibility and usefulness of modelling whole care pathways in NICE guidelines: a Prostate cancer case study

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NOT FOR QUOTATION



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Executive summary

Background

Clinical guidelines offer a unique opportunity for consistent decision making across a number of areas within a specific disease or condition. Modelling whole pathways of care may confer advantages over the traditional approach of modelling piecewise decisions.

Aims

The 2008 NICE guideline on prostate cancer is being considered for updating and is used as a case study. We will investigate the feasibility and value of whole pathway modelling of prostate cancer and the value of updating selected topics in the 2012 guideline update.

Methods

We developed a patient-level simulation model using Simul8, to capture the clinical pathway set out in the 2008 NICE Prostate Cancer Guideline. The boundary of our analysis mirrors the scope of the guideline, which starts at the point of referral into secondary care and follows patients until death. This baseline model will be modified to assess the cost-effectiveness of several potential alterations to the pathway that might be considered within an update of the guideline in 2012. We use evidence from the literature to populate the model with parameters to reflect the costs and effects of diagnostic tests and treatment options along the clinical pathway. Since the 2008 guideline, several new clinical studies have been published and these will be used in our analysis. The value of updating the topics will be judged on the basis of the incremental net benefit of the possible changes to the clinical pathway compared to the baseline model.

Findings/Conclusions

This project is still in progress. We will consider the value of this approach in modelling prostate cancer, and its wider application in modelling complex clinical pathways.

Introduction

Much attention has been paid to the methods of economic evaluation for technology assessment. These evaluations are necessarily framed around the intervention(s) at an isolated point in the clinical pathway. Clinical guidelines offer a unique opportunity for consistent decision making across a number of areas within a specific disease or condition as they typically address several questions at different points in the clinical pathway. Economic modelling in clinical guidelines developed by the National Institute for Health and Clinical Excellence (NICE) is generally confined to a few specific questions, using piecewise methods of economic evaluation.

It has been suggested that modelling whole pathways of care may confer advantages over the traditional approach of modelling discrete decisions in the pathway (Tappenden 2011). Modelling the whole pathway can allow the impact of upstream and downstream decisions to be assessed at each decision point along the pathway. It can also allow more than one decision to be evaluated using a single model and can overcome the inflexibility associated with modelling discrete topics if - as often happens - the relevant questions change over the lifetime of guideline development process (24 months).

The MAPGuide project aims to investigate the feasibility of modelling pathways recommended in NICE clinical guidelines and to illustrate how such models can be used as a basis for assessing the incremental cost-effectiveness of possible variations in the care pathway.

This paper looks in detail at one of the case studies developed for the MAPGuide project, for prostate cancer. We describe the development of a simulation model of the recommended care pathway for prostate cancer. This model is currently being finalised, and when completed will provide baseline estimates of overall patient flows, health outcomes and costs to the NHS if the guideline is followed. We discuss the potential to estimate value of updating each topic within the guideline, using the incremental net benefit of possible changes to the clinical pathway. Finally, we discuss the feasibility and potential usefulness of whole pathway modelling in NICE clinical guidelines and in other modelling complex clinical pathways.

Background

Clinical guidelines produced by the National Institute for Health and Clinical Excellence (NICE) are not mandatory, but they set standards for NHS care across England and Wales. As with other types of NICE guidance, they are based on the best available evidence on clinical and cost-effectiveness. However, not all the questions posed in a clinical guideline can be addressed using traditional methods of economic evaluation, due to time and analytical resource constraints. Potential topics for economic modelling are prioritised according to two main criteria: (1) the impact a potential change in practice might have in terms of health outcomes and/or healthcare cost, and (2) the likelihood that economic modelling will have an impact on decision making.

NICE clinical guidelines have been produced since 2001 and are published with the expectation that they will be reviewed, usually three years after publication, and updated as necessary. Updating existing guidelines now constitutes a major part of the Institute's work programme. In recent years the review process for deciding whether a guideline needs updating has been formalised. A review group is usually formed, made up of original members of the guideline development group who discuss whether there is new evidence which might change current recommendations. Stakeholders registered with NICE are invited to comment on a provisional review decision. If a decision to update the guideline is made, a formal scope is developed, which specifies the clinical questions to be addressed and to update. The review and scoping decisions are largely motivated by the state of the clinical evidence rather than any formal or quantitative assessment of the value of updating the topics within a guideline update.

Methods

A. Model existing pathway

Step 1: Preliminary literature review

We conducted a literature review on published economic models for the disease area and related models from NICE guidance (e.g. technology appraisals) and other HTA bodies and guideline developers. We searched the following secondary databases, using general disease/patient group search terms:

- CRD NHS Economic Evaluation Database
- CRD HTA Database
- NHS Evidence
- Cochrane Library
- Guidelines International Network database

This search was intended as a rapid means of identifying appropriate model structures and sources of data. We did not conduct formal critical appraisal of published economic evaluations, or summarise their findings, as this is of limited use for model development. Documentation for the current NICE guideline was reviewed in detail to ensure understanding of the recommendations and the care pathway, the available evidence and GDG rationale for decisions.

Step 2: Design the conceptual model

When designing an economic model, the purpose of the model (i.e. the question(s) it will be used to answer) is usually the starting point. Given that part of our research question was to gauge the flexibility of the model, we did not know the review questions we would want to evaluate at the outset. Instead we wanted to develop a model that would be capable of evaluating the cost-effectiveness of one or more changes to the pathway. We envisage the possible review questions will fall into one of the following categories:

- I. substitution of different tests or treatments at given points in the pathway
- II. addition of tests or treatments as an extra step in the pathway

- III. different sequencing of tests or treatments and/or
- IV. changes to patient eligibility criteria or thresholds for tests or treatments.

The baseline model captures what we considered to be the important features of the prostate cancer clinical pathway *if* the guideline recommendations were to be fully implemented. This does not necessarily reflect actual practice in the health service at the time of guideline development or now – the extent of implementation and compliance with guideline recommendations is likely to be variable. The model follows the NICE Reference Case (NICE Guide to the Methods of Technology Appraisal, 2008).

The scope of the original NICE guideline was used to define the boundaries of the model and to define entry/exit rules from guideline pathways. For example, although the guideline refers to the referral of patients with suspected prostate cancer from primary care, this is covered in another guideline (NICE, 2005) and is thus outside the model boundary. Conversely, men initially suspected of having prostate cancer but who do not have the disease may exit the model due to diagnosis of benign prostate hyperplasia (BPH) are covered by a separate guideline (NICE, 2011a) but lifetime costs and consequences accrued to these patients are included in the prostate cancer model.

Despite the prostate cancer guideline having a relatively clear structure it was difficult to interpret and translate individual recommendations into a coherent clinical pathway. We consulted an oncologist who was a member of the original guideline development group to help in this process and to make assumptions where there were gaps between recommendations in the guideline.

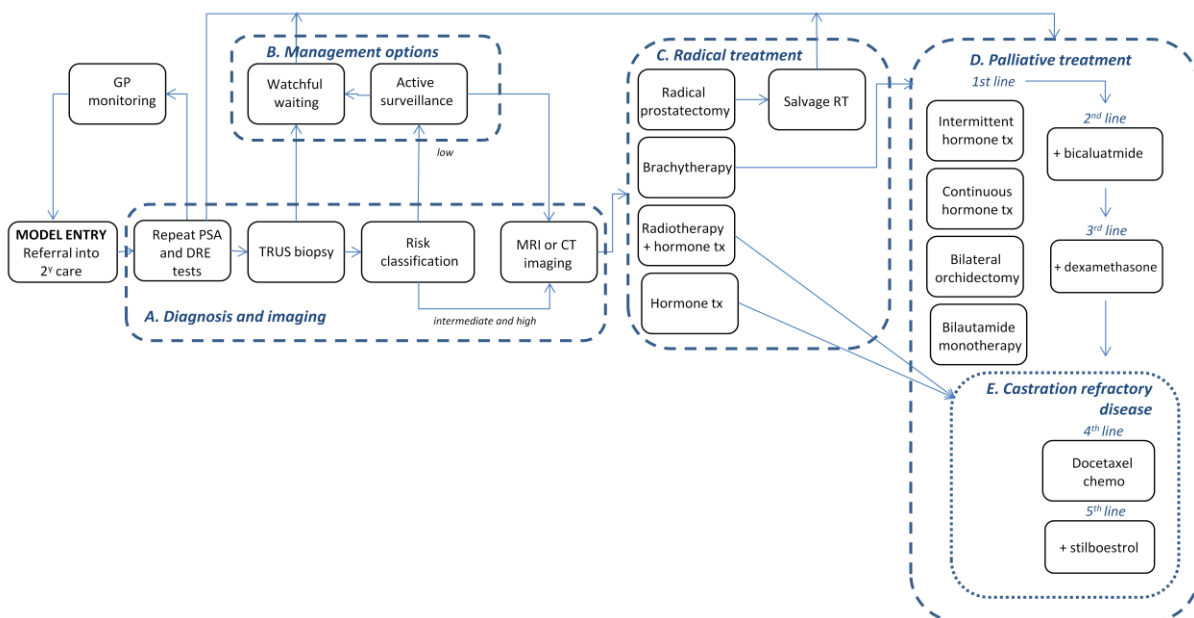


Figure 1: Summary of the clinical pathway

Patients enter the model having been referred to secondary care by their General Practitioner (GP), either due to the presence of symptoms or due to an elevated prostate specific antigen (PSA) test. A PSA test (blood test) and a digital rectal examination (DRE) will be repeated on entry into secondary care. Patients with obvious symptoms of advanced prostate cancer will be offered a bone scan and hormone treatment with palliative intent. All other men will be considered for a transrectal ultrasound guided biopsy. Patients for whom a biopsy is not considered necessary and those who opt out of biopsy will be referred back to the GP for monitoring (six monthly PSA test). These patients will not have a diagnosis of prostate cancer (although they may in fact have prostate cancer, or may go on to develop prostate cancer).

The biopsy gives the clinician information on the gleason score (a marker of cell differentiation or ‘aggressiveness’ of the cancer). If the biopsy is negative, the possibility of a re-biopsy will be discussed at a multi-disciplinary team meeting. These patients may be diagnosed with BPH, or referred back to the GP for monitoring. If the biopsy result is ‘suspicious’ but not diagnostic of cancer, the biopsy will be repeated, after a 6 month wait. If the biopsy is positive, but the patient is not considered suitable for radical treatment they will be offered hormone treatment with palliative intent if they experience any symptoms, or will be put on ‘watchful waiting’. Watchful waiting is a programme of monitoring by a secondary care clinician (even though the tests themselves may be carried out in a primary care setting) when a decision has been made to not pursue radical treatment. Disease progression and/or symptoms whilst on watchful waiting will result in hormone treatment being offered.

Patients who are suitable for radical treatment will have their risk of relapse (i.e. radical treatment failure) assessed according to the D’Amico risk classification system (see table 1 below). If patients have high risk disease, they will go for imaging with MRI (or CT if contra-indicated). There is no explicit recommendation in the guideline about the appropriateness of imaging for patients with intermediate risk disease, but we assume this will be done before radical treatment begins. Low risk patients will not receive imaging, and will be put on ‘active surveillance’ with 3-monthly PSA tests for the first year, 6-monthly thereafter and biopsies every 3 years. Active surveillance differs from watchful waiting in that it is intended for low risk men who do not have clinically significant disease. The aim of active surveillance is therefore to wait for the onset of clinically significant disease before beginning radical treatment which can be associated with harmful adverse events.

Table 1: Risk classification (D’Amico 1998)

	PSA (from blood test)	Gleason (from biopsy)	Clinical stage (based on DRE findings)	
Low	<10 ng/ml	≤ 6	T1-T2a	“localised disease”
Medium	10-20 ng/ml	7	T2b or T2c	
High	>20 ng/ml	8-10	T3-T4	“locally advanced disease”

Radical treatment is chosen on the basis of a patient's risk category as well as on the results of imaging. We did not model the role of imaging as it was difficult to capture both in descriptive terms and in terms of reliable data to populate the model. Instead imaging was included only as an additional cost prior to treatment. Men with intermediate risk disease are considered for radical prostatectomy (surgery), brachytherapy or radical radiotherapy with neo-adjuvant hormone therapy. Men with high risk disease will either be offered radical radiotherapy with neo-adjuvant hormone therapy or hormone therapy alone. Patients who receive radical radiotherapy and had a gleason score higher than 7 will have adjuvant hormone therapy. Similarly if their pelvis risk was greater than 15% they will receive pelvic radiotherapy. Each radical treatment is associated with three potential adverse events, bowel function, urinary function and sexual function.

Patients given radical treatment are treated with a curative intent, so some may never go on to develop more advanced disease (they will die of some other cause). A regular follow up schedule is defined (6 monthly PSA tests for the first two years, annual thereafter). If relapse is confirmed, only patients who have undergone radical prostatectomy are eligible for salvage treatment with radiotherapy. Otherwise, or on relapse or after salvage treatment, patients will be offered hormone treatment with palliative intent unless they have already received hormone treatment (these patients have castration refractory prostate cancer, CRPC). First line options include hormonal castration: intermittent LHRHa, continuous LHRHa, or bicalutamide monotherapy, or surgical castration (bilateral orchidectomy). When treatment fails (defined by biochemical recurrence) patients can go on to receive bicalutamide, dexamethasone, chemotherapy with docetaxel and prednisolone, and stilboestrol. End of life care will consist of bisphosphonates, treatment for obstructive uropathy, strontium-89 and other pain relief.

In order to estimate the health outcomes for patients diagnosed and treated according to the above care pathway, a model of the disease process is also required. This comprises a set of mutually exclusive health states defined by the available health-related quality of life (HRQL) data, were used to define the mechanisms for progression between these states (see the second column in Figure 2 below). We made the assumption of conditional transitions between the health states. Therefore in the model it is only possible for patients to die of prostate cancer if they have metastatic disease, and only possible to develop metastatic disease if they have first had local progression.

Step 3: Programme model

We adopted an patient-level simulation approach as it provided a flexible structure for mapping the complicated diagnostic and treatment pathway. The model was developed in Simul8 which, designed for simulation modelling, is reasonably intuitive and flexible in terms of the results that can be obtained from experimentation. There is also the potential to explore animation in Simul8, to aid communication of the model and its results.

The intention behind this type of model is to produce a realistic set of virtual patient histories, from which estimates of population mean costs and mean effects (e.g. QALYs) can be estimated (Barton et al, 2004). Interactions between patient level characteristics, the clinical pathway and relevant competing events are depicted in figure 2. Individual variation is considered at all relevant points in the model, within the limitations of the data available.

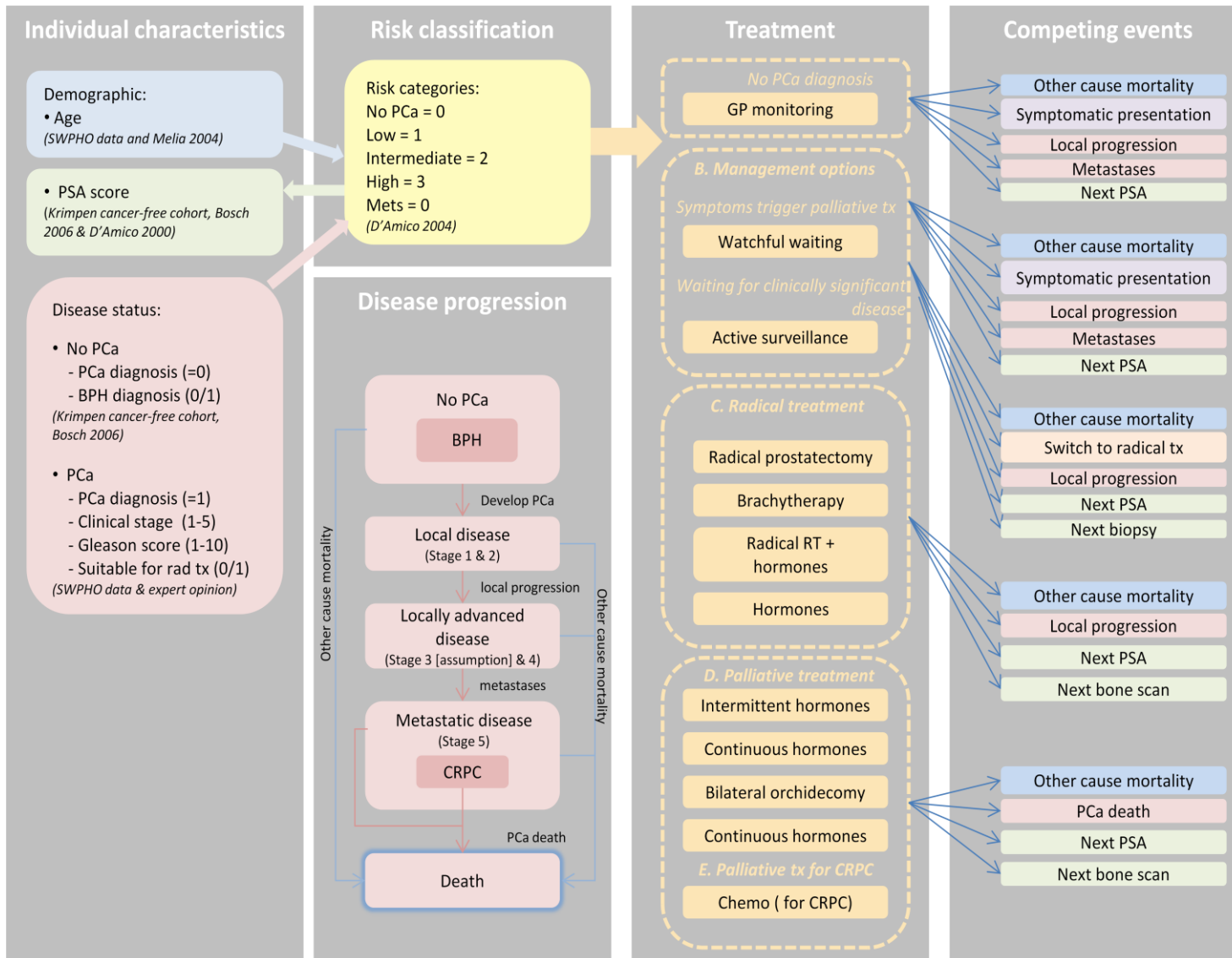


Figure 2: Interactions between patient characteristics, the disease process and the clinical pathway

The model was developed by considering the relevant competing events at each point in the clinical pathway (shown in the last column of figure 2). The method we used was to sample a time to each event and the earliest time determines which event happens next. This required a survival curve for each event and the assumptions that the events are both mutually exclusive and exhaustive. This method has the advantage that the individual survival curves for the events can be calculated independently of each other. The individual patient profiles were then updated (for example, age) and the times to the next events were re-calculated (by subtracting age from previously sampled time). This was then repeated for all hypothetical patients.

As transitions do not occur in fixed time periods, time was calculated separately as a summation of times between events. Costs and effects are not related to health states but are instead continuously calculated according to events. A continuous discounting approach was taken to account for social time preference of future costs and consequences.

We accounted for patient level variation within Simul8, when sampling from the survival curves or sampling a random number from a uniform distribution in the case of a probability. Sampling of second-order uncertainty for the probabilistic sensitivity analysis was implemented in Excel and read into Simul8. The model is then re-run 2000 times to propagate parameter uncertainty throughout the model.

Step 4: Populate model with data

To populate the model we used data from the original guideline, supplemented with new evidence identified through rapid literature searches and/or expert opinion. We did not conduct systematic reviews for all of these parameters, as this was not possible within the resources available for this study, neither would it be likely during routine guideline updates.

Key parameters include:

- Disease epidemiology: incidence and prevalence of the condition and subgroups, baseline risks, rates of progression of disease, mortality rates etc.
- Diagnostic accuracy (e.g. sensitivity and specificity) of any tests included in the pathway,
- Clinical effectiveness of any treatments included in the pathway,
- Utilities associated with disease, treatment and side effects,
- Resource use and unit costs

Disease epidemiology

Data were required to set initial characteristics of patients with prostate cancer and of patients without the disease (but being investigated due to a high PSA result in primary care). We used national cancer registry data obtained from the South West Public Health Observatory (SWPHO) to provide information age, clinical stage at diagnosis and Gleason score at diagnosis for patients with diagnosed prostate cancer. The national registry database does not record PSA score, so we calculated patients' risk according to two of the three D'Amico criteria (see Table 1) and used the PSA distribution for each risk category from a reported US cohort to define the patient's PSA score

on entry to the model (D'Amico 2009). This makes the assumption that this cohort accurately reflects the PSA distribution of patients in the UK when they enter secondary care.

Independent survival curves for local disease progression, metastatic disease progression and prostate cancer death were taken from the Bill-Axelsson randomised control trial (2011) comparing radical prostatectomy versus watchful waiting, as this was the nearest proxy to information on the natural history of the disease without treatment. A Metropolis Hastings calibration was run over four separate chains with different starting vectors in order to estimate plausible survival curves for each event, conditional on the population having experienced the previous event (the Bill-Axelsson RCT only reports independent survival curves for the whole population). For example, this allowed us to estimate time to developing metastases for patients with local progression.

Data on PSA scores of the cancer-free population were taken from Bosch (2006) which reports age-specific PSA distributions of the Krimpen longitudinal community-based study (in the Netherlands). By definition, these patients will not have a clinical stage and we assume they are the same age as patients with prostate cancer.

Disease prevalence in this population (men referred to secondary care with suspected prostate cancer) is hard to gauge, but we take age-specific prevalence estimates from data from a random sample of 87 GP practices in England in 2007 (Williams, 2011) which ranged from 3-6.1%. Data on death from causes other than prostate cancer were taken from 2007 national standard mortality rates, and adjusted by removing all deaths attributed to prostate cancer (C61) (ONS, 2010).

Test accuracy

We assume PSA, DRE, MRI, CT and bone scan are all perfect tests due the complexity of including the implications of false positive and false negatives results from these tests in the model. We assume that the transrectal ultrasound guided biopsy is associated with 100% specificity (ie. no false-positive results) as although this is unlikely, it is false-negatives rather than false-positives that are the major concern. Test accuracy studies are difficult to undertake in this area, since pathological confirmation will not be carried out on patients with negative biopsy results. We used a sensitivity of 77% (Rabbani, 1998). A very small proportion of patients will get an infection as a result of biopsy, 0.47% (Raaijmakers, 2002). Not all patients are prepared to undergo biopsy; we assume 12% men will opt out (Donovan, 2003). For the probabilistic sensitivity analysis, we assume these parameters follow beta distributions.

Clinical effectiveness

Where more than one treatment is recommended at a particular point in the pathway, we used proportions elicited from the department of health national radiotherapy group or experts on the original guideline development group. The management and treatment options in the model were grouped according to the clinical intent and the key outcome measures in the clinical studies (see Figure 2). Perhaps surprisingly there is a lack of comparative effectiveness of the radical treatments. Therefore through necessity, data from different trials each were used and compared against single arms of other trials (see Table 2 below). Radical prostatectomy is also associated with an excess mortality risk (Alibhai, 2006). The guideline recommends that clinically meaningful relapse should be

established before palliative treatment, but we could not find data to model the relationship between treatment, disease progression and PSA changes over time therefore we assume biochemical relapse after radical treatment is a proxy for local progression.

Table 2: Radical treatment data

Treatment	Model parameter	First-order uncertainty	Second order uncertainty	Source
Radical prostatectomy	Time to biochemical progression	weibull ($\alpha=0.62$, $\beta=182.67$)	Multivariate normal ($\log \lambda = -3.22$, $\gamma = 0.62$)	Giberti 2009 (radical prostatectomy vs. brachytherapy)
	Probability of sexual function AE	Uniform (0,1)	Beta ($\alpha = 60$, $\beta = 40$, mean = 0.6)	
	Probability of urinary function AE	Uniform (0,1)	Beta ($\alpha = 18.4$, $\beta = 81.6$, mean = 0.184)	
	Probability of bowel function AE	0	0	
Brachytherapy	Time to biochemical progression	weibull ($\alpha=0.846112974$, $\beta=2.80697845$)	Multivariate normal ($\log \lambda = -3.83$, $\gamma = 0.85$)	Giberti 2009
	Probability of sexual function AE	Uniform (0,1)	Beta ($\alpha = 42$, $\beta = 58$, mean = 0.42)	
	Probability of urinary function AE	Uniform (0,1)	Beta ($\alpha = 80$, $\beta = 20$, mean = 0.8)	
	Probability of bowel function AE	Not reported. In base-case analysis set equal to probability of bowel AE with radiotherapy.		Assumption, using Fransson 2009 (QoL data from SPCG7, Widmark RCT)
Adjuvant hormones +radical radiotherapy	Time to biochemical progression	weibull ($\alpha=1.354431605$, $\beta=21.78254729$)	Multivariate normal ($\log \lambda = -4.17$, $\gamma = 1.35$)	Widmark 2009 (adjuvant hormones + RT vs. hormones alone)
	Probability of sexual function AE	Uniform (0,1)	Beta ($\alpha = 250$, $\beta = 85$, mean = 0.75)	Fransson 2009
	Probability of urinary function AE	Uniform (0,1)	Beta ($\alpha = 64$, $\beta = 289$, mean = 0.18)	
	Probability of bowel function AE	Uniform (0,1)	Beta ($\alpha = 37$, $\beta = 312$, mean = 0.1)	
Hormone therapy alone	Time to biochemical progression	weibull ($\alpha=1.06$, $\beta=5.57$)	Multivariate normal ($\log \lambda = -1.82$, $\gamma = 1.06$)	Widmark 2009
	Probability of sexual function AE	Uniform (0,1)	Beta ($\alpha = 197$, $\beta = 110$, mean = 0.64)	Fransson 2009
	Probability of urinary function AE	Uniform (0,1)	Beta ($\alpha = 39$, $\beta = 289$, mean = 0.12)	
	Probability of bowel function AE	Uniform (0,1)	Beta ($\alpha = 23$, $\beta = 312$, mean = 0.07)	

Palliative treatment was also difficult to model as we found no trials which explicitly evaluated sequences of treatments. We assumed that first line palliative treatment is the sole determinant of overall survival (due to prostate cancer, the risk of other cause death is fixed). Subsequent lines of treatment only serve to increase the proportion of that survival that is 'progression-free'. This manipulation of the data requires that we ignore first order uncertainty in these parameters and use mean values for estimates of overall and progression-free survival. The uncertainty in these mean values is still captured in the probabilistic sensitivity analysis.

Table 3: Palliative treatment data

Treatment	Progression-free survival		Overall survival		Source	Comments
	Mean value (years)	Second order uncertainty	Mean value (years)	Second order uncertainty		
Intermittent hormones	7.4	Multivariate normal (log λ = -2.43, γ = 1.18)	7.0	Multivariate normal (log λ = -2.81, γ = 1.38)	Calais da Silva (2009)	
Continuous hormones	13.5	Multivariate normal (log λ = -2.37, γ = 0.92)	7.2	Multivariate normal (log λ = -2.22, γ = 1.11)	Calais da Silva (2009)	
Bilateral orchidectomy	3.6	Multivariate normal (log λ = -1.23, γ = 0.99)	3.4	Multivariate normal (log λ = -2.05, γ = 1.54)	PFS: Eisenberger 1998 OS: Seidenfeld 2000 meta-analysis	
Bicalutamide monotherapy	1.2	Multivariate normal (log λ = -0.52, γ = 1.61)	2.8	Log normal (ln(mean)=0.18, se=0.11)	Tyrrell 1998	Hazard ratio applied to bilateral orchidectomy baseline.
LHRHa + Bicalutamide	0.5	Normal (mean = 5.8 months, sd=0.2948)	n/a	n/a	Suzuki 2008	2nd line CAB, but pts have had 1st line CAB (no pts in our model have had this intervention).
LHRHa + dexamethasone	0.8	Multivariate normal (log λ =0.11, γ = 1.23)		Multivariate normal (log λ = -2.43, γ = 1.18)	Venkitaraman 2007	PFS curve was supplied on request.
Docetaxel + prednisolone	0.7	Multivariate normal (log λ =0.35, γ = 1.31)	1.7	Multivariate normal (log λ = -1.05, γ = 1.62)	Petrylak 2004	TAX327 used in NICE TA101 (Tannock, 2004) was not used as PFS was not measured in the trial.

Utilities

The lack of published utility data in prostate cancer has been widely acknowledged. The utility values used were identified in recent economic evaluations of prostate cancer (see table 4 below). No utility data published since was identified. We incorporate the impact on HRQL of the three most common adverse events attributable to radical treatment (bowel function, urinary function and sexual function) as disutilities. Given the absence of data on the duration of adverse events, we assume for the base case these last until local progression occurs, although we will explore this assumption using deterministic sensitivity analysis. The impact of adverse events on HRQL during palliative treatment was not captured.

Table 4: Utility data

Treatment	Mean utility value	Mean disutility value	Standard error (assumed)	Second order uncertainty	Source
Active surveillance	0.73	0.27	0.135	1- beta (4, 0.0675)	Hummel 2010
Radical treatment no AEs	0.78	0.22	0.11	1- beta (4, 0.055)	Hummel 2010
Sexual dysfunction	0.9	0.1	0.05	1- beta (2.6, 23.40)	Krahn et al. cited in <i>UK National Screening Committee (NSC) report</i> , Chilcott 2010
Urinary dysfunction	0.94	0.06	0.03	1- beta (2.76, 43.24)	Krahn et al. cited in <i>UK NSC report</i> , Chilcott 2010
Bowel dysfunction	0.89		0.04	beta (53.46, 6.61)	Krahn et al. cited in <i>UK NSC report</i> , Chilcott 2010
Biochemical recurrence	0.68	0.32	0.16	1- beta (4, 0.08)	Hummel 2010
Responsive metastatic disease	0.44	0.56	0.28	1- beta (4, 0.14)	Hummel 2010
Refractory metastatic disease	0.15	0.85	0.425	1- beta (4, 0.2125)	Hummel 2010

Resource use and unit costs

In accordance with the perspective of this analysis, the only costs considered were those relevant to the UK NHS. Costs were estimated in 2009-10 prices (since this is the price year from the most recent edition of NHS Reference costs, published January 2011). Resource use was estimated from the guideline recommendations (frequency of tests and follow up schedules etc.) and supplemented with expert opinion (details not shown here).

Table 5: Resource use

Treatment	Mean unit cost (£)	SE (estimated)	Distribution	Source
Urology consultant (first)	129	2.8	normal	NHS reference costs 2009-10, outpatient attendance
urology consultant (follow up)	88	1.6	normal	NHS reference costs 2009-10, outpatient attendance
Surgical consultant (first)	144	3.4	normal	NHS reference costs 2009-10, outpatient attendance
Surgical consultant (follow up)	100	2.3	normal	NHS reference costs 2009-10, outpatient attendance
Clinical oncology consultant (first)	166	6.7	normal	NHS reference costs 2009-10, outpatient attendance
Clinical oncology consultant (follow up)	101	3.8	normal	NHS reference costs 2009-10, outpatient attendance
Medical oncology consultant (first)	196	8.6	normal	NHS reference costs 2009-10, outpatient attendance
Medical oncology consultant (follow up)	128	3.9	normal	NHS reference costs 2009-10, outpatient attendance
Consultation diagnostic (first)	19	2.3	normal	NHS reference costs 2009-10, outpatient attendance
Admin oral chemo	152	10.4	normal	NHS reference costs 2009-10, HRG code SB11Z
Admin complex parenteral chemo (first)	271	8.5	normal	NHS reference costs 2009-10, HRG code SB13Z
Admin subsequent chemo	284	8.9	normal	NHS reference costs 2009-10, HRG code SB15Z
Radical prostatectomy (open)	4614	119.5	normal	NHS reference costs 2009-10, HRG code LB21Z
Bilateral orchidectomy	1398	33.8	normal	NHS reference costs 2009-10, HRG code LB34B

Radiotherapy planning	741	128.3	normal	NHS reference costs 2009-10, HRG code SC51Z
Radiotherapy delivery	129	6.0	normal	NHS reference costs 2009-10, HRG code SC23Z
Brachytherapy planning	1292	59.5	normal	NHS reference costs 2009-10, HRG code SC54Z
Brachytherapy delivery	802	44.3	normal	NHS reference costs 2009-10, HRG code SC26Z
Specialist erectile dysfunction services	1168	263.0	normal	NHS reference costs 2009-10, HRG code LB43Z
Post biopsy infection requiring hospitalisation	2387	83.587162	normal	NHS reference costs 2009-10, HRG code PA16B
PSA_1y care	11	2.21	gamma	estimate from Northern General Hospital, Sheffield in Hummel 2010
PSA_2y care	assume same as PSA in primary care (above)			
DRE	0	will be carried out as part of the consultation with the urologist		
TRUS biopsy	211.7185	12.45382984	normal	NHS reference costs 2009-10, HRG code LB27Z
CT	100.6544	2.246293632	normal	NHS reference costs 2009-10, HRG code RA08Z
MRI	173.5737	4.816671625	normal	NHS reference costs 2009-10, HRG code RA01Z
Bone scan	179.9243	6.947642835	normal	NHS reference costs 2009-10, HRG code RA36Z
Flexible sigmoidoscopy	210.9894	9.495922906	normal	NHS reference costs 2009-10, HRG code FZ54Z

Step 5: Verification and validation

Errors and inconsistencies were checked for throughout model development, following best practice for quality assuring simulation and decision analytic models. The model was verified internally (to ensure correct programming) and validated externally (to ensure consistency with expected results – for example, that survival times and levels of service use are realistic).

B. Model suggested pathway variations

A shortlist of possible topics for inclusion in an update of the guidelines was obtained from documentation about the NICE review of the guideline on their website. Each topic suggested a variation to the clinical pathway, which will be evaluated in comparison with the original pathway to estimate the incremental net benefit of the change for the relevant population.

Additional data required to derive these estimates will be obtained in the same way as data for the baseline model: from the original guideline, new evidence or by elicitation from experts. Probabilistic sensitivity analysis will then be used to estimate the extent of uncertainty over the net benefit estimates. Topics with a greater net benefit offer more potential for gain from a change in recommendations, and are thus a higher priority for inclusion in an update. All other things being equal, net benefits will be greater for topics that affect a large number of patients, offer a large health gain per patient and/or a small increase in costs.

Results

Work is still in progress, so we do not report the results here. However we can comment on the modelling potential of the nine shortlisted topics, in table 6 below. Figure 3 shows where these topics are located on the clinical pathway.

Table 6: Possible modifications to the clinical pathway

Topic	Type of question	Section of model	Proposed analysis
1. Pelvic radiotherapy with adjuvant hormonal therapy for men with high risk or locally advanced prostate cancer.	Type I: Substitute treatment	(C) Radical treatment	Can evaluate using existing model structure and data
2. Effective techniques for performing radical prostatectomy.	Type I: Substitute treatment	(C) Radical treatment	Increase granularity of pathway. Evaluation subject to available data.
3. High dose rate (HDR) brachytherapy in addition to external beam radiotherapy for men with localised or locally advanced prostate cancer.	Type I: Substitute treatment	(C) Radical treatment	Include treatment option in pathway. Evaluation subject to available data.
4. Low dose rate (LDR) brachytherapy in addition to external beam radiotherapy for men with localised or locally advanced prostate cancer.	Type I: Substitute treatment	(C) Radical treatment	Include treatment option in pathway. Evaluation subject to available data.
5. Degarelix (a LHRH antagonist), for men with advanced hormone dependent prostate cancer (locally advanced or metastatic).	Type I: Substitute treatment	(D) Palliative treatment	Include treatment option in pathway. Evaluation subject to available data.
6. Intermittent hormone therapy versus continuous hormone therapy for men with metastatic prostate cancer.	Type I: Substitute treatment	(D) Palliative treatment	Can evaluate using existing model structure and data
7. Radium 223 chloride versus strontium-89 for men with hormone refractory prostate cancer and painful bone metastases.	Type I: Substitute treatment	(E) Palliative treatment for men with CRPC	Include treatment option in pathway. May need to adapt structure of model to include potential survival benefit of radium-223 chloride. Evaluation subject to available data.
8. Active surveillance in previously unscreened 'low risk' men.	Type IV: change to patient eligibility criteria or thresholds for tests or treatment	Classification of risk – covers both (A) Diagnosis and imaging & (C) Radical treatment	Approach depends on how question is refined. May involve major modifications to model.
9. Intensity Modulated Radiation Therapy (IMRT) and Image Guided Radiation Therapy (IGRT) as an alternative to conventional therapy for men undergoing radiation treatment.	Type I: Substitute treatment	(C) Radical treatment	Increase granularity of pathway. Evaluation subject to available data.

At this stage the suggested topics are not very specific in terms of the intervention, its comparator and the relevant patient population: if included in an update, these broad topics would be refined in the scoping process and early stages of guideline development. For the purposes of our research study, the modellers will interpret the suggestions to define formal decision problems for analysis. The nine topic suggestions relate to four key variations to the clinical pathway: options for radical treatment, options for palliative hormone treatment, options for palliative treatment for men with hormone refractory prostate cancer and the classification of risk.

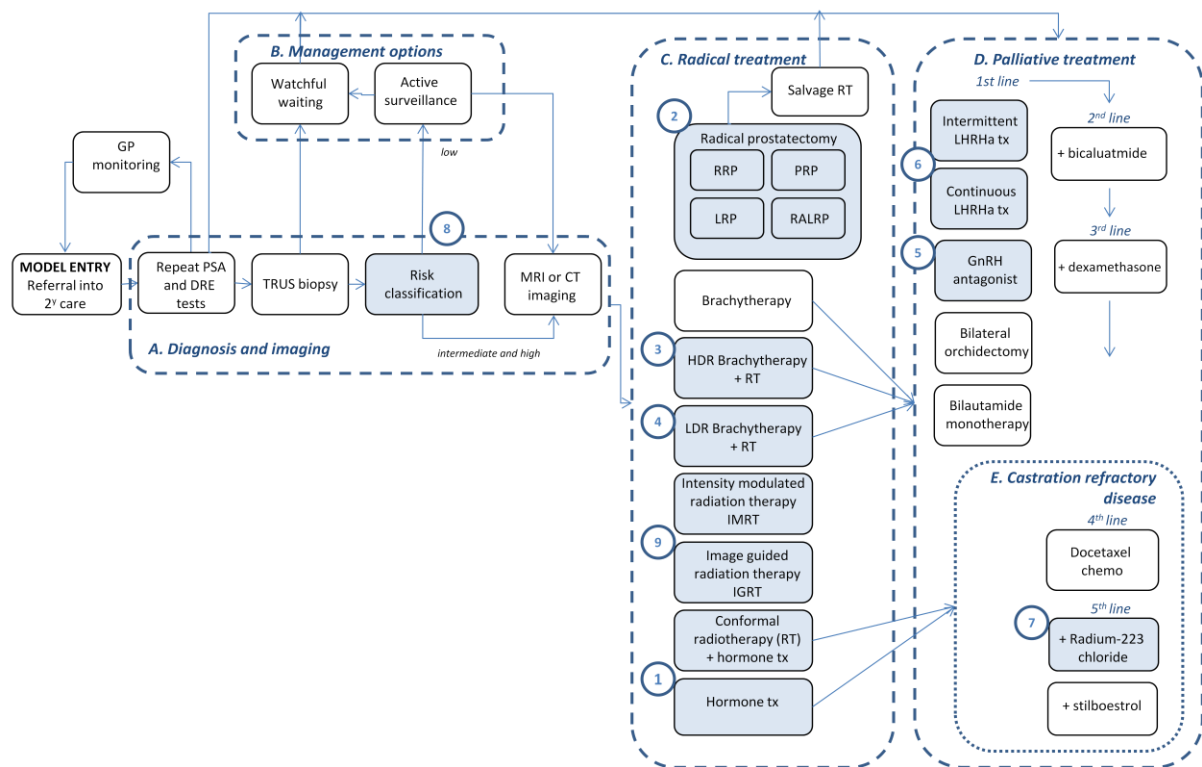


Figure 3: Location of topics in the clinical pathway

Pelvic radiotherapy with adjuvant hormones, intermittent hormone therapy and continuous hormone therapy (topics 1 and 6) are interventions which were recommended as appropriate treatment options in the 2008 guideline, but recent published clinical evidence may now support a stronger recommendation making a preference for one treatment over another. The cost-effectiveness of these topics can be evaluated using the current model structure and data.

Topic 8 is the most difficult topic to try to evaluate using our pathway model. This is because it is not clear how a subgroup of the patients with apparently low risk disease, but actually a more aggressive form of the disease can be indentified upfront. This is not so much a problem with evaluation within the structure of our model so much as a lack of a proposed solution to the problem. The question does not dictate how to differentiate between higher and lower risk people within the low risk category and the resulting pathways for each subgroup. If time allows, we will try to provide some information on the economic impact of various potential changes to the pathway by developing a scenario analysis.

Discussion

Despite not reporting the results of our analysis, (we think) modelling large portions of clinical pathways is possible at a reasonable level of resolution, using simulation modelling techniques. There are clear advantages of this approach over conventional piecewise modelling, particularly when faced with the multitude of decision problems posed in guideline development. Whole pathway modelling should enable the economic analysis of several questions to be addressed with the same model. The model developed for the 2008 prostate cancer guideline was used to answer

two questions on radical treatment, whereas it is likely that eight of the nine potential topics suggested in the prostate guideline update will be evaluated using the one pathway model.

Whole pathway models will also be attractive in situations when questions are posed after the model has been developed, for example at a later stage in guideline development. This is potentially very useful as the priority given to topics for economic analysis cannot always be predicted at the beginning of the guideline. Whole pathway models may also allow for more consistent decision making, as an assessment of how interventions in one part of the pathway influence other parts of the pathway can be made and decisions about different topics can be made simultaneously.

However, whole pathway models suffer from the same limitations inherent in all models. No amount of modelling would be able to mitigate the fact that no head-to-head trials compare all relevant radical treatment options, and that there are no data on sequential palliative treatment for patients with metastatic prostate cancer. Many assumptions were made in the conceptual modelling phase, in fact because we modelled the whole clinical pathway there were more choices be made by the analyst, resulting in some strong assumptions (for example, we assumed perfect accuracy for all tests apart from biopsy) which will inevitably restrict possible future uses of the model.

Whole pathway modelling is not synonymous with simulation, we could have used other methods such as systems dynamics to model the processes involved in the clinical pathway. A big advantage we foresee of using patient-level simulation models is that they are a more natural expression of the clinical pathway, and therefore the real-world experience of clinicians and patients. This may make the model more accessible to a clinical and lay audience and the use of 'patient vignettes' to demonstrate the running of the model on an individual basis holds great potential.

A patient-level simulation approach puts an additional demand on data. Access to individual-level data on patient characteristics at model entry is probably essential to fully characterise the correlations between the essential patient characteristics. We used UK cancer registry data on age, clinical stage and gleason score but did not have data on patients' PSA scores. Neither did we have data on the relationship between PSA score, underlying disease progression and treatment, which severely limited the way we were able to develop the conceptual model.

Patient-level simulation modelling is also associated with a greater computational burden than markov modelling, which limits the use of value of information analysis and expected value of perfect partial information (EVPPPI). We will need to consider further how to reflect decision uncertainty around current recommendations and the potential for resolving this uncertainty through a guideline update, as well as the clinical and economic importance of a potential change in recommendations.

Pathway models are a big investment – they are resource intensive and time-consuming to develop. However, we think there will be a big learning effect likely to make future development of pathways quicker and more efficient.

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