NETSCC, HTA

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Protocol for a systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localised prostate cancer

1. Background

Prostate cancer causes approximately 13% of cancer-related deaths and 4% of all deaths in the UK with an age-standardised mortality rate of 26/100,000; amounting to 10,000 men each year.[1] In the UK 35,000 new cases were reported in 2005.[1,2] 1997 the annual cost to the NHS was estimated at £55 million [3] whereas in 2007 the drug cost alone was approximately £130 million[4] and with added costs for surgery, radiotherapy, and hospital and community care the current annual cost is likely to exceed £200 million.

The largest rise in incidence seen recently is amongst relatively younger men as a consequence of case-finding and screening for asymptomatic disease.[5,6] using the serum marker, prostate specific antigen (PSA) and multiple trans-rectal ultrasound (TRUS) guided needle biopsies of the prostate.[5,6] The majority of these asymptomatic cancers appear confined to the prostate on clinical staging and are therefore amenable to cure through radical treatment.

Radical prostatectomy, whereby the prostate is completely removed surgically, remains the favoured curative treatment option for localised prostate cancer and has been demonstrated to improve disease-specific survival compared with watchful waiting, although this benefit takes 10 years to accrue.[7]

Open prostatectomy

Open radical prostatectomy involves the removal of the prostate gland together with the surrounding thin layers of connective tissue and is usually performed through a lower abdominal incision.[8] During the operation care is taken to minimise blood loss and to preserve the normal continence mechanism and, when tumour characteristics allow, the nerves and arteries supplying the penile erectile tissue. Despite this approximately 15% of men require blood transfusion, 7% have long-term urinary incontinence and 40% suffer erectile dysfunction after surgery although surgeons who perform larger numbers of cases tend to have better results[9,10] These longer-term adverse effects reduce men's general level of well-being and surgeons have therefore sought ways to reduce the functional disturbance of the procedure but maintain its disease-curing potential[11]

Laparascopic prostatectomy

Laparoscopic prostatectomy involves the insertion of five ports in the abdomen through which long, narrow instruments can be passed together with a camera. The ports are positioned ergonomically to enable the surgeon to dissect the prostate using the instruments with their handles located outside the body. Increasing experience with the technique has demonstrated that it does result in reduced blood loss compared to open prostatectomy but hoped for reduction in rates of erectile dysfunction and incontinence remains uncertain and is likely to depend on surgeon experience.[12-15]

Robotic prostatectomy

The use of robotic technology allows the surgeon to control the surgical instruments from a console. Robotic prostatectomy involves the preliminary insertion of an umbilical camera port and three other ports for the instruments controlled by the four robotic arms. Additional ports are used for instruments operated by a human assistant and maintenance of pneumoperitoneum. The procedure is then carried out in an identical fashion to laparoscopic prostatectomy but with the surgeon remotely controlling the three or four slave manipulator arms whilst seated at a console which is usually, although not necessarily, sited adjacent to the patient in the operating room.[16] Over recent years there has been a rapid expansion in the availability of the 'da Vinci®' robot to the NHS for radical prostatectomy. [17-19]

Rationale

The main advantage claimed for robotic prostatectomy is a reduction in the learning curve due to increased degrees of freedom of the robotic arms that hold the instruments.[20] However the impact of this has only been considered in one comparison,[21] in which the authors found that the direct costs associated with robotic procedures decreased substantially once their learning curve of 50 cases had been surpassed. Although the impact of more rapid gaining of competency on outcomes may be small, the impact on operating times, and hence on procedural costs might be significant and contribute to lower procedure costs in higher volume centres.[22,23] There is therefore a clear need to assess the relative clinical benefit and cost-effectiveness of laparoscopic and robotic prostatectomy in men with localised prostate cancer, including differential learning curve effects.

2. Aims and Objectives

The study aims to determine the clinical effectiveness and cost-effectiveness of robotic prostatectomy compared to laparoscopic prostatectomy in the treatment of patients with localised prostate cancer.

The specific objectives of the study are to:

- Describe clinical care pathways for laparoscopic and robotic prostatectomy in a UK context;
- Determine the clinical effectiveness and safety of each procedure;
- Determine the influence of the learning curve on estimates of effectiveness and safety;
- Perform a systematic review of existing economic evaluations of each procedure;
- Determine which procedure is most likely to be cost-effective for implementation into the UK NHS; and
- Identify future research needs.

3. Methods

3.1 Eligibility criteria

Types of study

We will consider evidence from randomised controlled trials (RCTs), non-randomised comparative studies and case series, the latter primarily for estimates of rare adverse events and longer-term effects. For estimating learning curve effects, information on the robotic or laparoscopic arms of comparative studies will be treated as case series. Systematic reviews of open prostatectomy will be considered in order to obtain evidence on the clinical effectiveness of open prostatectomy for the purposes of informing the economic model. We will include conference abstracts and non-English language reports of comparative studies only.

Types of participants

The types of participants considered will be men with localised prostate cancer, defined as cancer confined to the prostate gland and considered curable by radical removal of the prostate.

Types of interventions and comparators

The intervention considered will be robotic prostatectomy and the comparator laparoscopic prostatectomy. Open prostatectomy will also be considered as a comparator in studies comparing robotic prostatectomy with open prostatectomy, or laparoscopic prostatectomy with open prostatectomy, in order that such studies can be included in a mixed treatment

comparison model assessing the relative effectiveness of robotic and laparoscopic prostatectomy.

Types of outcome measures

The following types of outcome measures will be considered:

- Cancer related

Rate of positive margin in resected specimen, according to consensus definition;[24]

Biochemical (PSA) recurrence, defined as two successive PSA levels ≥ 0.4 ng/ml;[25]

and

Disease free survival, defined as absence of clinically detectable disease.

Death

- Functional

Recovery of sexual (penile erection) function , quantified by validated score (IIEF-5); and

Urinary continence, defined as use of ≤ 1 thin pad per day and/or validated symptom score.

- Adverse events

Peri-operative:

Blood loss – quantified as transfusion rate;

Conversion to open procedure;

Delayed discharge; and

Death.

Long term:

Anastomotic stricture.

Two surgeons will categorise each complication using the Clavien – Dindo Classification of Surgical Complications (Appendix 2)[26] with a third surgeon acting as arbitrar.

- Procedural

Learning curve;

Equipment failure;

Operative time;

Hospital stay; and

Duration of catheterisation.

- Patient-driven

Pain, quantified by validated pain score and analgesic requirements;

Productivity (time to return to full activity); and

Generic and disease-specific quality of life, measured through validated quality of life scores.

Exclusion criteria

The following types of report will be excluded:

- Studies of men with metastatic disease;
- Case series of open prostatectomy.

3.2 Search strategy

Comprehensive electronic searches will be conducted to identify reports of published studies. Highly sensitive search strategies will be designed, including appropriate subject headings and text word terms, interventions under consideration and included study designs. There will be no language restriction but searches will be restricted to years from 1995 onwards, reflecting the introduction of the techniques. Medline, Medline In Process, Embase, CINAHL, Biosis, Science Citation Index, Cochrane Controlled Trials Register (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Review of Effects (DARE) and the HTA databases will be searched. Reference lists of all included studies will be scanned in order to identify additional potentially relevant reports. We will also ask our expert panels to provide details of any additional potentially relevant reports.

Conference abstracts for the years 2006 onwards from meetings of the European, American and British Urological Associations will be searched. Ongoing studies will be identified through searching Current Controlled Trials, Clinical Trials, NIHR Portfolio and WHO International Clinical Trials Registry. Websites of manufacturers, professional organisations, regulatory bodies and the HTA will be checked to identify unpublished reports.

3.3 Quality assessment

We will use a modified version of the Cochrane risk of bias tool[27] which we have adapted to include potential topic-specific confounders, which were identified through discussions with members of our project advisory group and our knowledge of existing literature. The topic-specific confounders related to specific outcomes as shown in the modified risk of bias tool

(Appendix 3). Three sets of two reviewers will independently assess the risk of bias of included full text studies, with the exception of non-English publications and conference abstracts. Any differences in assessment or issues of uncertainty will be resolved by discussion and consensus. For the risk of bias tool individual outcomes will be scored as High risk of bias, Low risk of bias or Unclear. Any disagreements will be resolved by consensus or by a third party.

3.4 Data extraction

Three reviewers will independently screen titles and abstracts of all identified items. Full text copies of all potentially relevant reports will be obtained and independently assessed by two reviewers to determine whether they meet inclusion criteria. Three reviewers will independently extract details of study design, methods, participants, interventions and outcomes onto a data extraction form (see Appendix 1). Each reviewer's data extraction will be independently checked by a second reviewer for errors or inconsistencies. Any disagreements will be resolved through consensus or arbitration by a third party.

3.5 Data analysis

Data from each study will be tabulated and summarised for each procedure in a form appropriate for the mixed treatment comparison model. The lack of RCT evidence precludes undertaking a standard meta-analysis. Therefore we intend to adopt an indirect comparison (cross design) approach allowing inclusion of non-randomised comparative data and case series.[28] Reasons for heterogeneity of effects will be explored, including differences in populations, studies, outcome assessment and learning curve effects. We will examine heterogeneity between and within different study designs using a Bayesian hierarchical random effects model enabling use of all available evidence.[29]

We will use a previously successful approach developed by members of our project team to estimate the learning effects on key outcomes.[30] The expertise of the participating surgeons or centres in each included study will first be categorised by previous experience. Data on the three key features of learning: starting level, rate of learning and expert level will then be extracted. A random effects meta-analysis will be performed to estimate the pooled effect of the key features together with an appropriate measure of uncertainty. These estimates will be used to determine the likely "shape" of the learning curve and will be validated by our experienced and novice clinical experts. The pooled data will be used firstly to investigate heterogeneity of effects on the key outcomes in the systematic review of effectiveness and secondly to inform

the economic modelling on the likely change over time on the key outcomes and patient mix. This approach will account for possible differences in an individual surgeon's learning curve for particular outcomes.

4. Cost-effectiveness

4.1 Systematic review of economic evaluations

Given that the results of any economic evaluation are particular to setting and time the main purpose of a review is to inform the modelling methodology and any parameter sources. This does not require a systematic review, but a review of *key sources* i.e. those with a signal of high quality such as HTA reports. Therefore, there will be two reviews, a systematic one detailed below to identify the current status of the evidence on the technologies of interest and one of HTA reports, their citations and sources citing them looking at any technology for prostate cancer that uses modelling.

Search strategy

Highly sensitive search strategies will be designed to identify any economic evaluations where at least one of the technologies was laparoscopic or robotic surgery for prostate cancer. The following databases will be searched without language restriction for the years 1995 onwards: NHS EED, HTA Database, Medline, Medline In Process, Embase, Science Citation Index and Health Management Information Consortium (HMIC) database. Websites of HTA organisations will be consulted for additional reports. Reference lists of all included studies will be scanned and appropriate experts will be contacted for details of additional reports.

Quality assessment

Quality will be assessed according to the BMJ criteria, on which the NHS EED abstracts were largely based.[31]

Data extraction

Two reviewers will independently screen the titles and abstracts of all items identified by the search strategy. Full text copies of all potentially relevant reports will be obtained and assessed by two reviewers independently against the inclusion criteria. Any disagreements will be resolved by consensus or arbitration by a third person. Two reviewers will independently extract details of study design such as economic perspective and type of analysis, methods such as

model structure and costing, population, technologies, and outcomes such as QALYs onto specific data extraction forms in line with the NHS EED abstracts.

Reporting

Summaries of all studies will be tabulated. A brief critique according to model structure, paramaterisation and dealing with uncertainty will then be performed to identify methods that can be used together with, limitations and recommendations for improvement that can be taken forward to the proposed model. Any sources of evidence of possible use in the proposed model will be recorded and reviewed by the research team.

4.2 Economic evaluation

Implications for the economic analysis

As no prior economic evaluation has been conducted from the perspective of the UK NHS we propose to construct a decision analytic model (DAM) comparing the cost-effectiveness of the two surgical techniques, which will make the best use of the evidence obtained from the systematic review[32] A novel aspect of this work will be the emphasis on the learning curves for surgical procedures and economies of scale from changes in centre volumes which are likely to drive differences in costs for the considered technologies, something that in a typical CEA as recommended by NICE [33] might be ignored. These particular facets are likely to be instrumental in driving differences in costs for the considered technologies and therefore need to be accorded greater weight in the analysis. In addition to this the impact of capital costs (approximately £1.5 million) and maintenance costs (approximately £150,000/year) for robotic prostatectomy are likely to be significant, particularly in lower volume centres. Changes from the recommended standard procedure would take time to implement, and require more intensive re-training involving use of mentors which, although associated with a briefer learning curve,[34] may have additional resource implications and therefore require consideration in the model.

Model structure

In order to incorporate the effect of disease progression and possible need for subsequent treatments for each patient undergoing laparoscopic or robotic prostatectomy, a state transition model will be used which estimates consequences for a cohort beginning treatment at the same time. However, in order to estimate effects due to the learning curves for laparoscopic and robotic techniques a multiple cohort analysis will be used.[35,36] Such an approach, by allowing for changing numbers of patients eligible for surgery over time, also permits estimation of capital

outlay as a function of demand, which was the approach used in a previous model.[37] However, even if demand remains constant, it also allows availability of technology, which is a function of surgeon competence, to be expressed as a function of patient numbers. This also enables consideration of the most efficient number of treatment centres. A multiple cohort approach additionally allows for population heterogeneity in age; those who are eligible for treatment will vary by age[38] requiring the introduction of one cohort per age band per year. Although the technologies will be assumed to have a finite lifetime decided by manufacturer and clinical expert opinion and tested in a sensitivity analysis, each individual cohort will be followed up for various periods including the duration of patient lifetime in order to account for consequences for that cohort.[39]

The design for the state transition model used for each cohort, informed by expert opinion and published models of the progression of prostate cancer[40-42] is shown in Appendix 4, figures one to six. Patient eligibility is defined according to:

1. Male.
2. Cancer localised to Prostate

These criteria, including age will thus define an initial pre-operative state. A patient will then undergo one of the procedures whereby a set of short term complications can occur according to corresponding probabilities each of which are assumed to be resolved within a the cycle time of 3 months. Micro-simulation[43] will be used to analyse the model whereby an individual follows a random path over a lifetime using Monte Carlo Simulation (MCS). This reduces the need to define a separate health state of each of the set of criteria used to define a health state e.g. presence or absence of each complication. Therefore, subsequent health states will be defined according to the following set of state variables:

1. Age
2. Margin (positive or negative)
3. Postoperative Gleason score (high or low)
4. Recurrence (none, local, systemic)
5. Erectile dysfunction (present or not)

6. Urinary incontinence (present or not)

Therefore transition probabilities (probability of moving to some health state in 3 months given current health state) will be defined according to the status of each of the state variables. For example, mortality rate increases with age and type of recurrence. Also, as can be seen in the care pathway, further treatments also depend on state variables so that, for example, the presence of urinary incontinence implies treatment for this condition. Post operative evaluation of the surrounding tissue may lead to further treatment conditional on determining a positive or negative margin (Fig. 2). Where tissue margins are observed to be positive, then Gleason scores are used to identify an appropriate treatment within the pathway. Patients with high Gleason scores are immediately referred for further cancer treatment, whereas patients exhibiting low Gleason scores are monitored for BCR. Should BCR be observed, patients may then devolve to additional treatment for cancer, otherwise surveillance will continue. Patients with a negative margin will be referred for surveillance with the possibility of further cancer treatment if necessary.

Pathways for treatments available to patients with prostate cancer are described in figure 3. The treatment of localised cancers devolves into curative or palliative sub-pathways. Each sub-pathway may then lead to dysfunctions associated with the underlying condition and treatment. Ultimately, patients will reach a state of resolution or death. In the case of resolution of cancer, patients may then still be treated for the presence of one or more dysfunctions (Fig. 4 - 5). Patients may suffer from one or more dysfunctions simultaneously. In either case, interventions strategies may vary according to the severity of dysfunction. Ultimately, a patient may recover or reach a persistent state.

The economic perspective will be that of the United Kingdom National Health Service and discounting in the base case will be at 3.5%.[33] All modelling will pay attention to best practice[44] and guidance from the project expert advisory group. The model will be constructed in two software packages according to best practice[44] in C for speed and flexibility and TreeAge for presentation including any sensitivity analysis on demand.

Costing

Given the variation in costs due to learning and requirement for capital expenditure, it is essential to estimate the independent effect of staffing, equipment and overheads. As described above, some costs will be incurred as each patient progresses through the care pathway and thus would count as *variable* (with demand). However, a machine (and any additional building space) must be purchased regardless of numbers to be treated at least beyond the capacity of any existing machine. Therefore such a cost is fixed at least in the short term. The most appropriate sources will be used for each of these, such as expert opinion to determine appropriate staff mix, the systematic review to estimate operation times and length of stay as a function of technology, and purchase/maintenance costs from manufacturers and local users and their finance departments. Unit costs will be taken from appropriate routine sources for staffing,[45] British National Formulary for drugs, and from equipment manufacturers. Variability in parameters will be tested by one-way sensitivity analyses.

Utilities

A cost utility analysis (CUA) will be performed with outcomes estimated in quality-adjusted life years (QALYs).[46] Each health state of the state transition model will require a utility estimated using the best available data, ideally derived using EQ-5D.[47-50] If necessary, plausible assumptions will be made in order to use utility values derived from different patient population (e.g. using an additive model to combine the effects of disease progression and adverse events in one age group to estimate the effect in a different age group).

Epidemiology

Two main items of epidemiological data are required for the economic model; one at the individual level to estimate the transition probabilities of the state transition model and another at the population level for the incidence of eligible patients. The former will be based on data from the systematic review and include any effect of surgeon experience/learning. The latter will be informed by incidence data and any likely trends informed by expert opinion. Each parameter will correspond to transitions between states in the model, such as from first treatment to remission.

Uncertainty

Deterministic sensitivity analyses will be carried out to test for the effect of assumptions and variability.[51] Costs and QALYs will be estimated as the expectation over the joint distribution of the parameters, informed from the systematic review, other sampling distributions or expert

opinion according to best practice. Any correlations, informed where possible by the systematic review, will be incorporated. A probabilistic sensitivity analysis will also be undertaken allowing presentation of results in a series of cost-effectiveness acceptability curves (CEAC) and the construction of the cost-effectiveness acceptability frontier (CEAF) for various threshold values of the willingness to pay (WTP) for a QALY.[52]

Identification of future research needs

A value of information analysis[53] will be conducted to identify the expected value of perfect information (EVPI) over the expected lifetime of the considered procedures and the value of further research to identify more precise and reliable estimates of parameters used in the model.

5. Timescale

Start of project: 1st March 2010

Develop protocol and data extraction form: March - April 2010

Run search strategies: April 2010

Assess studies for inclusion: April – June 2010

First expert panel meeting: May 2010

Data extraction and quality assessment: July – September 2010

First progress report: 10 October 2010

Data analysis: October – December 2010

Second expert panel meeting: February 2011

Economic modelling: May 2010 – March 2011

Second progress report: February 2011

Report writing: January – April 2011

Report submission: 16th May 2011

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Version 6, 7th February 2011

Appendix 1. Data extraction form for the systematic review of clinical effectiveness of robotic prostatectomy versus laparoscopic prostatectomy in the treatment of localised prostate cancer

Data Extraction Form

Clinical effectiveness of robotic prostatectomy versus laparoscopic prostatectomy in the treatment of localised prostate cancer

Reviewer ID: Data extraction date:

Study ID (Author, year): Language if non-English:

Publication status: full-text papers / conference abstract / personal communication / other unpublished reports (specify)

Study IDs of any linked reports:

Study design

Aim of the study:

Study design:

☐ RCT ☐ Non-randomised comparative study ☐ Registry report

☐ Case series ☐ Prospective ☐ Retrospective ☐ Unclear ☐ Systematic review (open prostatectomy)

For comparative studies, comparison:

☐ Robotic prostatectomy *versus* laparoscopic prostatectomy

☐ Robotic prostatectomy *versus* open prostatectomy

☐ Laparoscopic prostatectomy *versus* open prostatectomy

☐ Other comparison, specify:

For case series or registry, intervention:

☐ Robotic prostatectomy

☐ Laparoscopic prostatectomy

Number of study centres: Single centre / multicentre (specify number of centres) / not reported

Setting: hospital / other (specify) Country:

Study start – end dates: Duration of study:

For non-RCTs and case series, was patient recruitment consecutive: Yes /No / not reported

Length of follow-up:
Source of funding:
Additional information on study design: Prospective/retrospective/not reported For comparative studies, patients in the groups were recruited during the same period/different period/not reported

Patients				
Inclusion criteria:				
Exclusion criteria:				
Baseline Patient Characteristics				
	Intervention 1: **Robotic**	Intervention 2: **Laparoscopic**	Intervention 3: **Open**	Total
Number of patients enrolled				
Randomised (RCTs only)				
Withdrew/lost to follow-up, with reasons				
Number analysed				
Age (Mean/median, SD/range)				
BMI (Mean/median, SD/range)				
Co-morbidities, including previous abdominal or pelvic surgery, previous pelvic radiotherapy, n/N (%), specify				
Disease severity	--	--	--	--
PSA level, ng/ml, n, mean(SD) / median (range) /categorical				
Clinical stage, T1/T2/T3, specify staging method, e.g. digital rectal examination, MRI				
Biopsy Gleason Score ≤ 6, n 7, n 8-10, n				
Prostate size, ml, mean (SD) / median (range)				
Erectile dysfunction, n/N (%), specify measure and validated or not:				

Intervention

Intervention 1: **Robotic prostatectomy**

Trade name and manufacturer of robot:

- ☐ da Vinci system by Intuitive Surgical Inc., Sunnyvale, California, USA
- ☐ Other, specify:
- ☐ Not reported

Model number(s):

Surgical approaches:

- ☐ Intra-peritoneal
- ☐ Extra-peritoneal
- ☐ Not reported

Location of the operator console:

- ☐ In the same room
- ☐ An adjacent room
- ☐ Off-site, specify
- ☐ Not reported

Nerve sparing for erectile function:

- ☐ Unilateral, n/N
- ☐ Bilateral, n/N:
- ☐ Non- nerve sparing
- ☐ Not reported

Lymph node dissection:

- ☐ No
- ☐ Yes, details:
- ☐ Not reported

Additional information:

Intervention 2: **Laparoscopic prostatectomy**

Trade name, manufacturer, and model number of laparoscopic equipment:

Surgical approaches:

- ☐ Intra-peritoneal
- ☐ Extra-peritoneal
- ☐ Not reported

Nerve sparing for erectile function:

- ☐ Unilateral, n/N
- ☐ Bilateral, n/N:
- ☐ Non- nerve sparing
- ☐ Not reported

Lymph node dissection:

- ☐ No
- ☐ Yes, details:
- ☐ Not reported

Additional information:

Intervention 3: **Open prostatectomy**

Nerve sparing for erectile function:

☐ Unilateral, n/N ☐ Bilateral, n/N: ☐ Non- nerve sparing ☐ Not reported

Lymph node dissection:

☐ No ☐ Yes, details: ☐ Not reported

Additional information:

Urinary incontinence				
Safety outcomes				
☐ > 1 thin pad per day, n/N (%)				
Peri-operative	Timing, e.g. 6wks, 1mo, 3mo, 1 year after surgery	Intervention 1: **robotic**	Intervention 2: **laparoscopic**	Intervention 3: **open**
☐ Other measures, e.g. subjective measure, specify				
Equipment failure, n/N (%)				
Erectile dysfunction,				
☐ International Index of Erectile Dysfunction				
Converted to other intervention, e.g. open operation, n/N (%), specify the route				
☐ Other measures, specify, and validated or not				
Blood transfusion requirement, n/N (%)	--			
Operating time, minutes, n, mean (SD) / median (range)				
Faecal incontinence, n/N (%), specify measure and validated or not:				
Hospital stay (recovery time), days, n, mean (SD) /median (range)				
Re-admission, days, n, mean (SD) /median (range)				
Need critical care, number of patients				
Efficacy outcomes				
Bladder neck stenosis / anastomotic stricture, n/N (%)	Timing, e.g. 6wks, 1mo, 3mo, 1 year after surgery	Intervention 1: **robotic**	Intervention 2: **laparoscopic**	Intervention 3: **open**
Duration of catheterisation, days, n, mean (SD) /median (range)				
Anastomotic leak, n/N (%)				
Positive margin in resected specimen, n/N (%), specify definition:				
Hernia into port sites or incision sites, n/N (%)				
Infection, n/N (%), specify site				
Pathology stage, pT1/pT2/pT3, specify staging method, e.g. digital rectal examination, MRI				
Organ injury, e.g. bowel, blood vessels, n/N (%), specify				
Pathological Gleason Score ≤ 6, n				
7, n				
8-10, n				
Ileus, n/N (%)				
Deep vein thrombosis, n/N (%)				
PSA recurrence, n/N (%), specify definition, e.g. two successive PSA levels ≥ 0.4 ng/ml):				
Pulmonary embolism, n/N (%)				
Other peri-operative outcomes, n/N (%), specify				
Local recurrence, n/N (%)				
Port site recurrence, n/N (%)				--
Metastatic disease, n/N (%)				
Dysfunction				
Required further treatment & death				
Any dysfunction including urinary, faecal, or erectile, n/N (%)				
Further cancer treatment, n/N (%) in total				
Curative treatment, n/N (%)				
Resolved or died, n/N (%)				
Palliative treatment, n/N (%)				

Resolved or died, n/N (%)				
Curative and palliative treatment, n/N (%)				
Resolved or died, n/N (%)				
Treatment of urinary incontinence, n/N (%)	**			
Resolved or persistent, n/N (%)				
Treatment of faecal incontinence, n/N (%)				
Resolved or persistent, n/N (%)				
Treatment of erectile dysfunction, n/N (%)				
Resolved or persistent, n/N (%)				
Death in total, n/N (%), specify causes				
Quality of life outcomes				
Time to return to full activity, n, mean (SD) / median (range)				
Quality of life (QoL): ☐ Generic QoL, specify measure (validated) used: ☐ Disease-specific QoL, specify measure (validated) used: ☐ Other validated measures, specify:				

Procedural outcomes			
Time taken to perform the procedure at the end this study, minutes, mean (SD) / median (range)	Intervention 1: **robotic**	Intervention 2: **laparoscopic**	Intervention 3: **open**
Procedures done in the centre each year, mean (SD) / median (range)			
Surgeon competence (learning curve), by surgeon and by centre	--	--	
Number of surgeons			
Number of procedures conducted before this study			
Number of procedures conducted during this study			

Additional information, e.g. description about the experience of the surgeons			

Appendix 2. Clavien – Dindo Classification of Surgical Complications

Grade	Definition	Exclusions
Grade 0	No deviation from planned post-operative course considering procedure and pre-existing co-morbidity	
Grade I	Any deviation from the normal postoperative course without the need for specific pharmacological treatment or surgical, endoscopic and radiological interventions. This grade **includes** the following general non-scheduled interventions: ▪ Antiemetics ▪ Antipyretics ▪ Analgesics ▪ Diuretics ▪ Electrolyte replacement ▪ Physiotherapy ▪ Ward management of wound infection	
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.	Treatments listed under **Grade I**
Grade III a	Requiring surgical, endoscopic or radiological intervention **not under** general anaesthesia	
Grade III b	Requiring surgical, endoscopic or radiological intervention **under** general anaesthesia	
Grade IV a	Life-threatening complication affecting **single** organ system requiring IC/ICU-management	Transient ischaemic attacks (TIA)
Grade IV b	Life-threatening complication affecting **more than one** organ system requiring IC/ICU-management	Transient ischaemic attacks (TIA)
Grade V	Death of a patient	
Additional suffix: d	Complication requiring continued management after discharge from hospital	

Dindo D., Demartines N., Clavien P.A.; Ann Surg. 2004; 244: 931-937
http://www.surgicalcomplication.info/index-2.html

Appendix 3. Cochrane risk of bias table (non-randomised studies)
Laparoscopic versus robotic prostatectomy for localised prostate cancer

Assessor initial: **Date evaluated:**
Study ID:

Item			**Judgement** [a]	**Description** (quote from paper, or describe key information)
1. Sequence generation				
2. Allocation concealment				
	Outcome 1 (peri-op safety)	**Confounders balanced** [b]		
	Surgeon experience			
	Co-morbidity (ASA/Charlson score)			
	Prostate size			
	Outcome 2 (urinary dysfunction)	**Confounders balanced** [b]		
3b. Confounding [b]	Surgeon experience			
	Age			
	Neurovascular bundle excision			
	Anastomotic stricture			
	Outcome 3 (erectile dysfunction)	**Confounders balanced** [b]		
	Pre-op dysfunction/status			
3c. Confounding [b]	Neurovascular bundle excision			
	Surgeon experience			
	Age/Co-morbidity			
	Outcome 4 (efficacy)	**Confounders balanced** [b]		
3d. Confounding [b]	Gleason score balanced at baseline			
	Surgeon experience			
	PSA score balanced at baseline			

Item			Judgement [a]	Description (quote from paper, or describe key information)
		Clinical [b1] tumour stage/nodal stage balanced at baseline		
4a.	Blinding?	Outcome 1 (peri-op safety)		
4b.	Blinding?	Outcome 2 (urinary dysfunction)		
4c.	Blinding?	Outcome 3 (erectile dysfunction)		
4d.	Blinding?	Outcome 4 (efficacy)		
5a.	Incompl. outcome data addressed?	Outcome 1 (peri-op safety)		
5b.	Incompl. outcome data addressed?	Outcome 2 (urinary dysfunction)		
5c.	Incompl. outcome data addressed?	Outcome 3 (erectile dysfunction)		
5d.	Incompl. outcome data addressed?	Outcome 4 (efficacy)		
6a.	Free of selective reporting?	Outcome 1 (peri-op safety)		
6b.	Free of selective reporting?	Outcome 2 (urinary dysfunction)		
6c.	Free of selective reporting?	Outcome 3 (erectile dysfunction)		
6d.	Free of selective reporting?	Outcome 4 (efficacy)		
7.	Free of other bias?			
8.	*A priori* protocol? [c]			
9.	*A priori* analysis plan? [d]			

[a] Some items on **low/high risk/unclear scale** (single line border), some on **yes/no/unclear scale** (dashed border). For all items, record "unclear" if inadequate reporting prevents a judgement being made.

[b] Confounders listed by order of importance (high to low importance)

Low risk:
4 balanced = low risk
3 balanced, 1 unbalanced = low risk
3 balanced, 1 unclear = low risk
2 balanced, 1 unbalanced, 1 unclear = low risk
2 balanced, 2 unclear = low risk

High risk:
4 unbalanced = high risk
3 unbalanced, 1 balanced = high risk
3 unbalanced, 1 unclear = high risk
2 unbalanced, 2 balanced = high risk
2 unbalanced, 1 balanced, 1 unclear = high risk
2 unbalanced, 2 unclear = high risk

Unclear:
4 unclear = unclear
3 unclear, 1 balanced = unclear
3 unclear, 1 unbalanced = unclear

[b1] or pathological stage balanced in absence of clinical stage information.

NB. If confounders are imbalanced but adjusted for in the analysis, the imbalance is no longer a serious concern for risk of bias.

[c] Based on list of confounders considered important at the outset and defined in the protocol for the review (*and assessment against worksheet - optional*)

[d] Did the researchers write protocol defining the study population, intervention and comparator, primary and other outcomes, data collection methods, etc. in advance of starting the study?

[e] Did the researchers have an analysis plan defining the primary and other outcomes, statistical methods, subgroup analyses, etc. in advance of starting the study?

General Decision Rules

Where there a paper does not report details of confounders/other source of bias this should be judged as unclear.

Where a paper does not report considered outcome this should be judged as not applicable.

Allocation concealment should be judged as high risk of bias if groups are allocated by factors such as surgeon decision, patient preference. Allocation by hospital/institution = low risk. Where no details are given, judge as unclear.

Surgeon experience: Assume surgeons performing open prostatectomy are experienced unless stated otherwise.

Absence of blinding is likely to have low risk of bias for peri-operative and efficacy outcomes.

Free of other bias: default is low risk unless there is a fundamental flaw with the study (e.g. inadequate follow up time for dysfunction outcomes, data not presented for learning curve effects if these are likely to influence outcomes).

Judging overall direction of bias for individual outcomes: If confounding is judged unbalanced, outcome should be judged as high risk of bias.

Studies for which RoB tool is intended
Only suitable for 'cohort-like' studies, individually or cluster-allocated. Include secondary analyses of clinical databases providing the analysis is clearly structured as a comparison of control and intervention participants. Refer to Ch.13, tables 13.2.a and b:

Table 13.2.a: individually allocated study designs
- RCT – randomised controlled trial
- Q-RCT – quasi randomised controlled trial
- NRCT – non-randomised controlled trial
- CBA – controlled before and after study (not common use of this label, see CChBA below)
- PCS – prospective cohort study
- RCS – retrospective cohort study

Table 13.2.b: cluster allocated study designs
- ClRCT – cluster randomised controlled trial
- ClQ-RCT – cluster quasi randomised controlled trial
- ClNRCT – cluster non-randomised controlled trial
- CITS – controlled interrupted time series
- CChBA – controlled cohort before and after study (Shadish, Cook & Campbell)

Assessment of risk of bias
Issues when using modified RoB tool to assess cohort-like non-randomised studies:
- Use existing principle: score judgement and provide information (preferably direct quote) to support judgement
- Additional item on confounding.
- 5-point scale for <u>some</u> items (distinguish "unclear" from intermediate risk of bias).
- Keep in mind the general philosophy – assessment is <u>not</u> about whether researchers could have done better but about risk of bias; the assessment tool must be used in a standard way whatever the difficulty / circumstances of investigating the research question of interest and whatever the study design used.
- Use of 5-point scale is uncharted territory; very interested to know whether this makes things easier or more difficult for reviewers.
- Anchors? "1/No/low risk" of bias should correspond to a high quality RCT. "5/high risk" of bias should correspond to a risk of bias that means the findings should not be considered (too risky, too much bias, more likely to mislead than inform)

1. Sequence generation
   - Low/high/unclear RoB item
   - Always high RoB (not random) for a non-randomised study
   - Might argue that this item redundant for NRS since always high – but important to include in RoB table ('level playing field' argument)
2. Allocation concealment
   - Low/high/unclear RoB item
   - Potentially <u>low</u> RoB for a <u>non-randomised study</u>, e.g. quasi-randomised (so high RoB to sequence generation) but concealed (reviewer judges that the people making decisions about including participants didn't know how allocation was being done, e.g. odd/even date of birth/hospital number)
3. RoB from confounding (<u>additional item for NRS; assess for each outcome</u>)

- Assumes a prespecified list of potential confounders defined in the protocol
- Low(1) / 2 / 3 / 4 / high(5) / unclear RoB item
- Judgement needs to factor in:
    - proportion of confounders (from prespecified list) that were considered
    - whether most important confounders (from prespecified list) were considered
    - resolution / precision with which confounders were measured
    - extent of imbalance between groups at baseline
    - care with which adjustment was done (typically a judgement about the statistical modelling carried out by authors)
- Low RoB requires that all important confounders are balanced at baseline (not primarily/not only a statistical judgement OR measured 'well' and 'carefully' controlled for in the analysis.

We have provided an optional 'worksheet' to help reviewers to focus on the task (rows=confounders and columns=factors to consider). Reviewers could make a RoB judgement about each factor first and then 'eyeball' these for the judgement RoB table.

4. RoB from lack of blinding (assess for each outcome, as per existing RoB tool)
    - Low(1) / 2 / 3 / 4 / high(5) / unclear RoB item
    - Judgement needs to factor in:
        - nature of outcome (subjective / objective; source of information)
        - who was / was not blinded and the risk that those who were not blinded could introduce performance or detection bias
        - see Ch.8
5. RoB from incomplete outcome data (assess for each outcome, as per existing RoB tool)
    - Low(1) / 2 / 3 / 4 / high(5) / unclear RoB item
    - Judgement needs to factor in:
        - reasons for missing data
        - whether amount of missing data balanced across groups, with similar reasons
        - see Ch.8
6. RoB from selective reporting (assess for each outcome, NB different to existing Ch.8 recommendation)
    - Low(1) / 2 / 3 / 4 / high(5) /unclear RoB item
    - Judgement needs to factor in:
        - existing RoB guidance on selective outcome reporting
        - see Ch.8
        - also, extent to which analyses (and potentially other choices) could have been manipulated to bias the findings reported, e.g. choice of method of model fitting, potential confounders considered / included
        - look for evidence that there was a protocol in advance of doing any analysis / obtaining the data (difficult unless explicitly reported); NRS very different from RCTs. RCTs must have a protocol in advance of starting to recruit (for REC/IRB/other regulatory approval); NRS need not (especially older studies)
        - Hence, separate yes/no items asking reviewers whether they think the researchers had a prespecified protocol and analysis plan?

Appendix 4. Model Structure

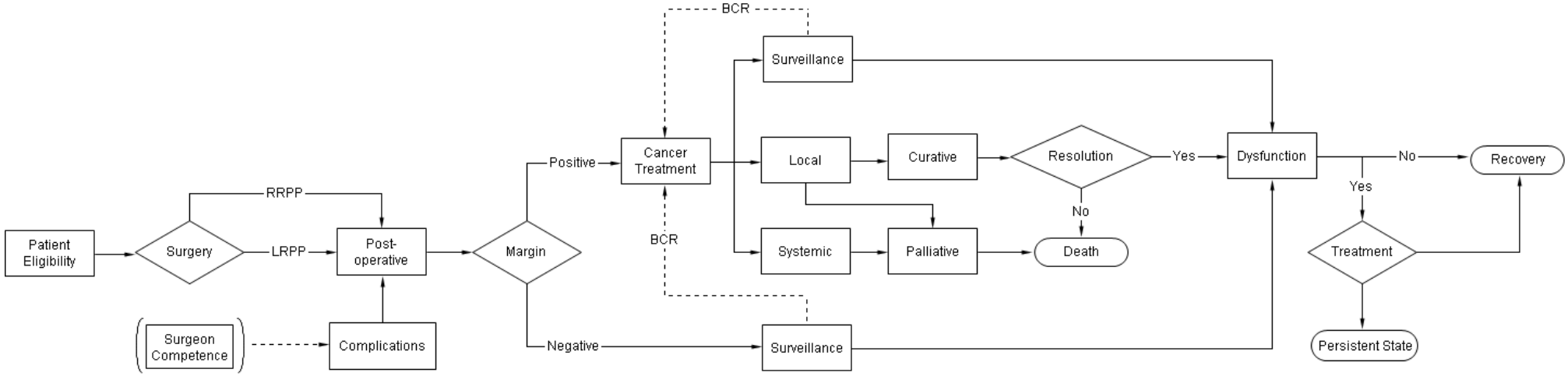

Figure 1. Summary pathway

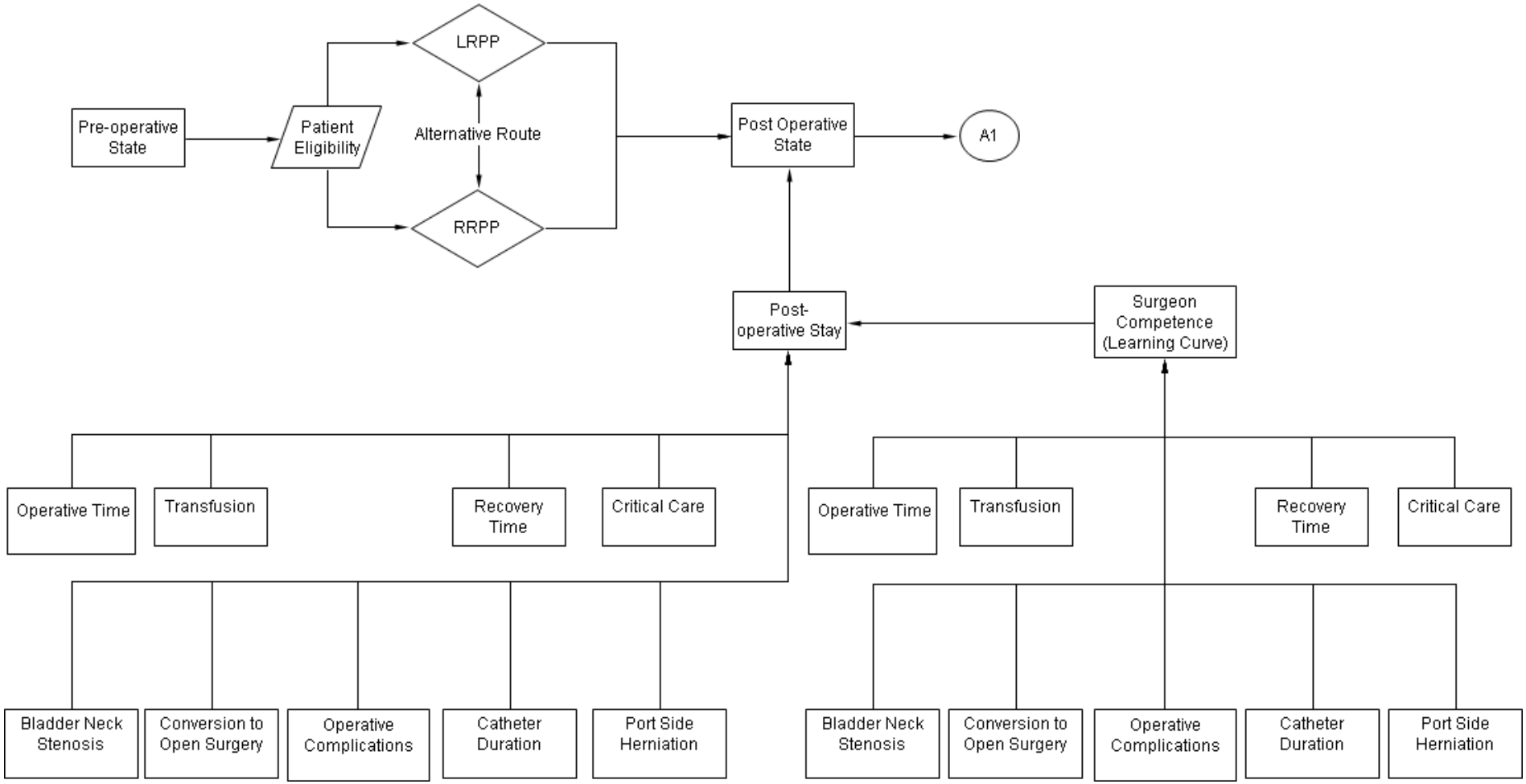

Figure 2. The pre-operative state defining patient characteristics and eligibility for each surgical procedure; the pathway describes the progression of an individual following either surgical procedure and illustrates factors likely to influence their post operative state.

Patient characteristics and eligibility are defined as:

1. Male, age and BMI
2. CaP localised to Prostate.
3. Prostate size.
4. Clinical stage: T1/2, T3a/T3b, T4
5. Erectile dysfunction.
6. Gleason Score ≤ 6.
7. Fit for General Anaesthetic.
8. Suitable Hospital Infrastructure.

The potential for operative complications may act independently on the post-operative condition and as a function of the relative experience of each surgeon within a treatment centre. Each patient may exhibit multiple complications simultaneously, each driving impacting upon the cost effectiveness of treatment (Fig. 1).

Post operative evaluation of the surrounding tissue may lead to further treatment conditional on determining a positive or negative margin (Fig. 2). Where tissue margins are observed to be positive, then Gleason score are used to identify an appropriate treatment within the pathway. Patients with high Gleason scores are immediately referred for further cancer treatment, whereas patients exhibiting low Gleason scores are monitored for BCR. Should BCR be observed, patients may then devolve to additional treatment for cancer, otherwise surveillance will continue. Patients with demonstrating a negative margin will be referred for surveillance and the possibility of further cancer treatment is necessary.

Pathways for treatments available to patients with prostate cancer are described in figure 3. The treatment of localised cancers devolves into curative or palliative sub-pathways. Each sub-pathway may then lead to dysfunctions associated with the underlying condition and treatment. Ultimately, patients will reach a state of resolution or death. In the case of resolution of cancer, patients may then still be treated for the presence of one or more dysfunctions (Fig. 4 - 5). Patients may suffer from one or more dysfunctions simultaneously. In either case, interventions strategies may vary according to the severity of dysfunction. Ultimately, a patient may recover or reach a persistent state.

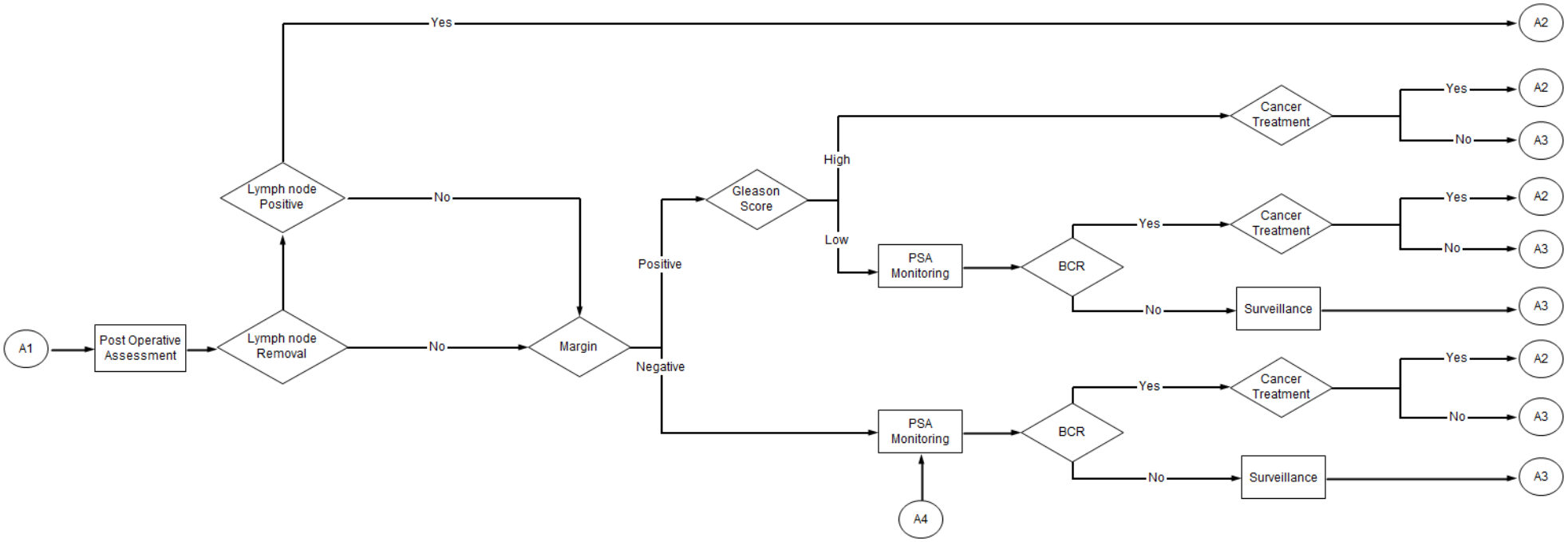

Figure 3. The above pathway illustrating the progression of patients through post-operative assessment and the allocation of further treatment or continued surveillance.

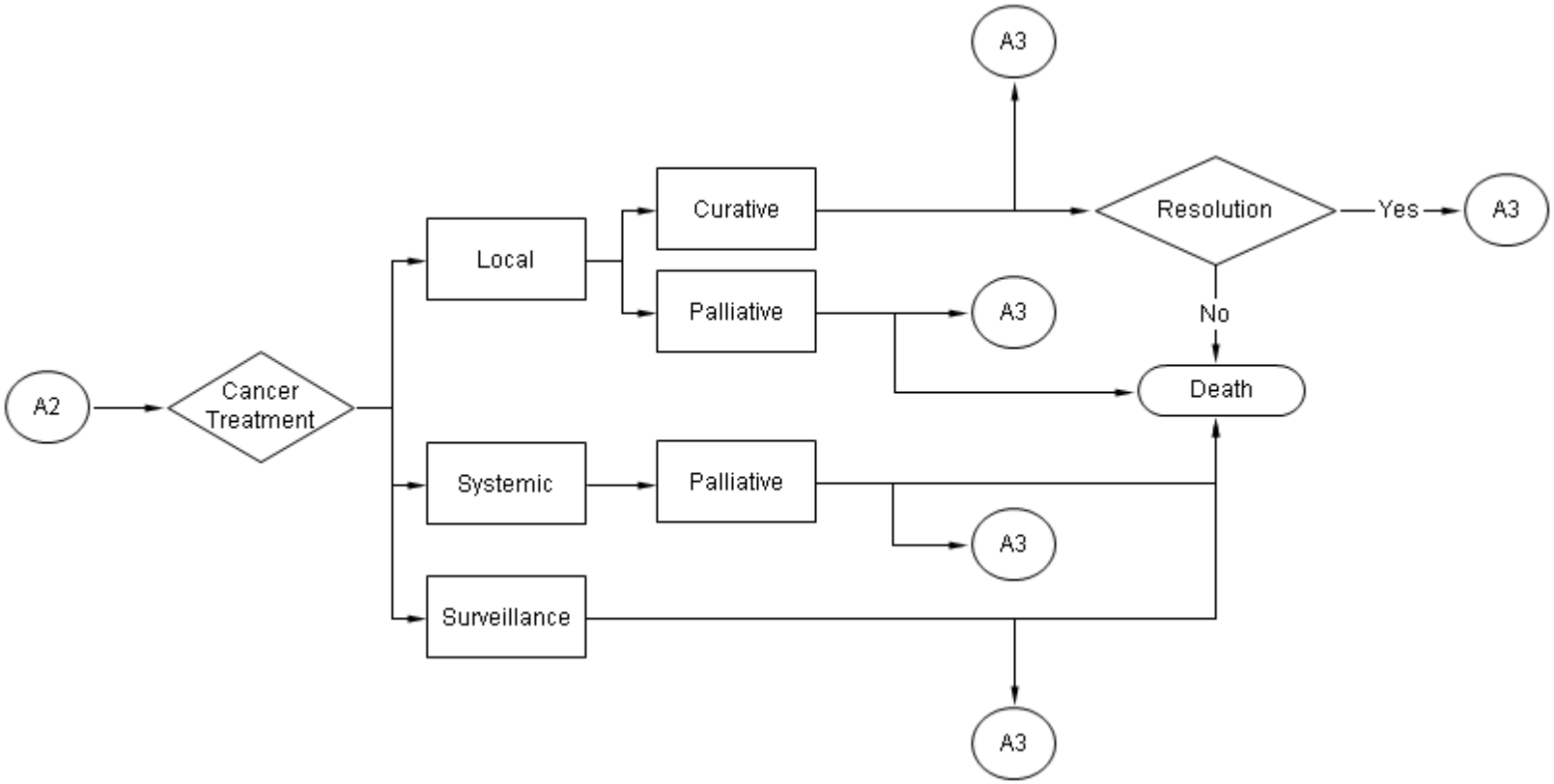

Figure 4. Illustrates the treatment options for patients identified as still suffering from cancer. Cancer treatment may take one of three forms, namely local, systemic and continued surveillance.

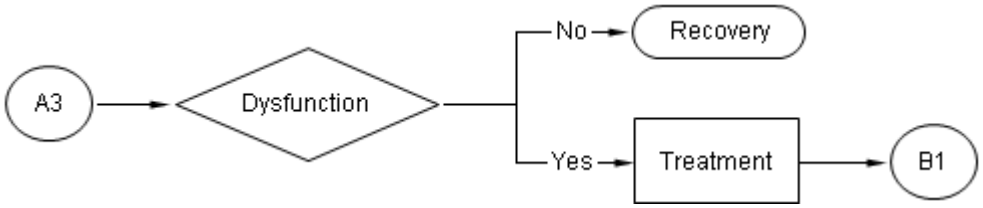

Figure 5. Describes the pathway for the treatment of dysfunctions.

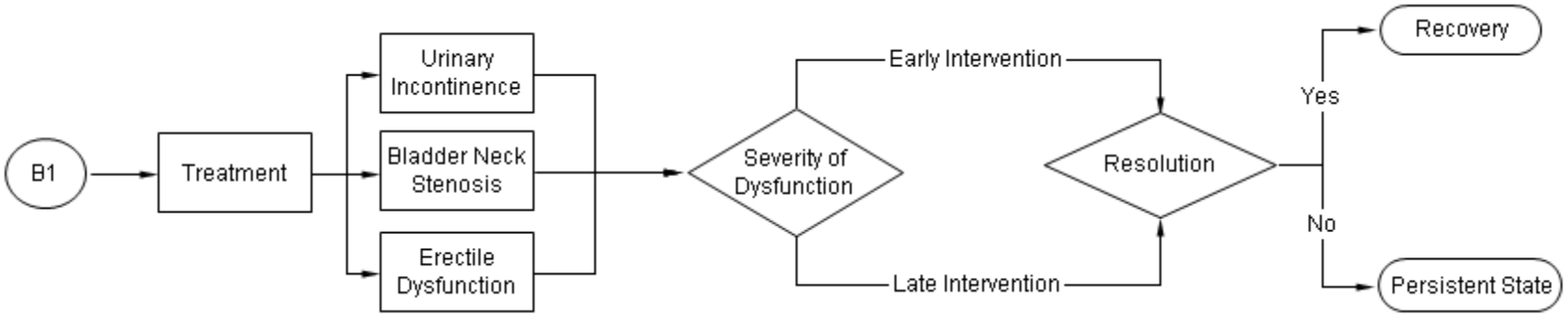

Figure 6. Treatment pathway for dysfunctions. Patients may suffer from one or more dysfunctions simultaneously.