

LAPPRO

LAParoscopic Prostatectomy Robot Open

A randomised, open study of radical prostatectomy with or without lymphadenectomy as part of a prospective, non-randomised, open comparative study of robot assisted laparoscopy and open radical prostatectomy.

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1. ORGANISATION

1.1 Planning committee:

Bo Anderberg, Professor, Karolinska Institute

Ingela Björholt, PhD, Sahlgrenska Akademin

Jan-Erik Damber, Professor, Sahlgrenska Akademin

Eva Haglind, Professor, Sahlgrenska University Hospital/ Sahlgrenska Academy

Jonas Hugosson, Professor, Sahlgrenska Academy

Elisabet Lindholm, ML, Sahlgrenska University Hospital

Gunnar Steineck, Professor, Onkology Centre/ Sahlgrenska Academy

Peter Wiklund, Professor, Karolinska Institute

The committee started working in 2005 and is responsible for the design of the protocol

1.2 Principal investigator:

Eva Haglind

1.3 Deputy principal investigator:

Gunnar Steineck

1.4 Study secretariat:

Sahlgrenska University Hospital and Oncology Centre, Göteborg

1.5 Study steering committee:

Eva Haglind, Gunnar Steineck, Jan-Erik Damber, Jonas Hugosson, Peter Wiklund, "post.doc" MD Johan Stranne and the local investigators at the participating hospitals (if other than those mentioned above) and a monitoring nurse.

The committee meets at least twice per year and whenever a committee member indicates that a meeting is necessary.

1.6 Monitoring:

Responsibility: Eva Haglind via research nurse

Ongoing follow-up and control of data collection as well as adherence to the protocol through communication with the respective local investigators. Visits to the participating hospitals if necessary. Responsibility for patient reminders in regard to questionnaires.

1.7 Writing committee:

Active members of the planning committee, local investigators from participating hospitals and active researchers involved in the principal study or part thereof.

No results will be analysed during the study. No partial results with comparisons between the study groups will be published. Only the study design and level of inclusion can be presented during the ongoing study. Participating hospitals can analyse questions in their own data, but the LAPPRO steering committee will be informed via the PI and will discuss analysis design before it takes place.

The primary and secondary aims of the study as described in this protocol will be analysed after the inclusion and follow-up in accordance with the protocol. Publication refers to international peer reviewed scientific journals. The steering committee will decide if reporting at relevant international conferences takes place and by whom.

Customary protocol regarding co-authorship will be observed.

2 PROTOCOL

2.1 Background

Diagnosis of early prostate cancer has increased noticeably during the last 10 years and this has resulted in more men being offered curative treatment. The number of radical prostatectomies in Sweden has increased from a couple of hundred to more than two thousand per year. This number will probably increase further over the next five years.

The only randomised study so far, SPCG-4, showed a significant difference in mortality at follow-up after 8.2 years. The mortality rate from prostate cancer was 14.4 percent in the control group who had no surgery but who were followed actively ("watchful waiting"), and 8.6 percent in the group who had radical prostatectomy, analysed as "intention to treat" [1]. Mortality, independantly of the cause, changed from 32 percent to 27 percent [1]. Thus the absolute effect of surgery is 5 percent both for deaths from prostate cancer and total mortality and twenty men must have surgery to prevent the early death of one. This figure includes a large proportion, close to three quarters, of the men who were diagnosed with prostate cancer when they sought help regarding problems with micturation. These days when many men are diagnosed without micturation problems but after health checks for Prostate Specific Antigen (PSA) in the blood, the number is certainly higher, i.e. more than twenty men must have surgery to save one man from premature death. The knowledge that radical surgery of prostate cancer improves survival, has resulted in surgery becoming the most common form of treatment for early prostate cancer, not only in Sweden but in most countries. A very rough estimate indicates that two million men world-wide have had a radical prostatectomy, despite the cited study showing large numbers of patients experiencing ongoing complications. A comparative study is currently being done in the USA and a study in England includes surgery, radiation treatment and active monitoring. The oncological results from these studies will not be available for 5-10 years.

The treatment aims to radically remove the tumor and thus increase the proportion of patients surviving 10 years without recurrence, the "oncologic result". Good surgical technique means that the proportion of patients where the tumor is totally excised ("radical surgery") must be high, or the primary aim of the operation is jeopardized. At the same time the technique must be as "atraumatic" as possible to minimize the risk for complications. The most serious impairments for the patient are incontinence and impotence. Increased experience has improved surgical technique and the risk of such damage has decreased. The number of patients with lasting impotence and/or incontinence after the operation is still high. The risk of developing an inguinal hernia after open radical prostatectomy is reported to be higher than expected [2].

Based on the expected survival effects and remaining life expectancy in different age cohorts, the radical operation is these days offered to patients with tumors limited to the prostate gland ("early tumors") and who have a long life expectancy, often with an upper age limit of 70 years. The aim is to carry out surgery with a short stay in hospital, a short recovery period and low risk of subsequent illness. This ameliorates patient suffering and lessens the cost to individuals and to society.

Unpublished data from the study shows that with adjustment for the number of symptoms "watchful waiting" decreases quality of life, indicating that the diagnosis in itself causes psychological damage (1). There is a clear link between the number of symptoms and self identified quality of life and also between the number of symptoms and a feeling of wellbeing. The nearly linear correlation indicates that a decrease in the portion of men with sexual impotence or urinary leakage after surgery will improve their self identified quality of life and wellbeing. Unpublished data also shows that the quality of life decreases dramatically for castrated men in the group under "watchful waiting" but not for the men in the group who had a radical prostatectomy.

Approximately 10 years ago it was suggested that laparoscopy would result in better results than the open surgical technique. This was based on the possibility that the laparoscopic technique means better lighting, improved enlargement and makes it possible for the entire surgical team to follow the operation. It also means that the operation is carried out with instruments in the cramped space inside the lower pelvis. A laparoscopic technique was developed and adopted in a small number of urological centres round the world. Reports have described long operations and long training times for surgeons [3, 4]. There are also reports of decreased numbers of complications. There are no prospective, comparative or randomised studies, and the level of knowledge does not allow any conclusions to be drawn. There are no reports of long term outcomes. The technical difficulties have prevented the technique being widely used.

Robot assisted laparoscopy technique has been used for some years to carry out radical prostatectomies. The use of this technique retains all the theoretical advantages of laparoscopy with the addition of three-dimensional images and more degrees of freedom in the use of the instruments. In theory this should be an advantage, not least while working inside the lower pelvis, where there is always a lack of space particularly in males. The published results from individual surgeons and departments point to possibly fewer complications than the published results of open surgery [5-7]. There are no evaluations of this technique in randomised or prospective comparative studies. Despite this the robot assisted technique is

increasingly being used for radical prostatectomies, according to promising preliminary reports, both regarding the number of patients with impotence/incontinence and the portion of patients where radicality has been achieved [8, 9]. Compared to laparoscopy the robot assisted laparoscopy technique means a shorter learning period and also shorter surgery times compared to classic laparoscopy [10]. The published reports also indicate the possibility of decreased bleeding during surgery and shorter hospital stays [6].

As well as the advantages described above there are possible disadvantages, which have not been scientifically evaluated. The technique is only about five years old and potential technique specific complications are completely unknown. The robot does not produce so called "haptic feedback" which means that tactile sensation is lost. The value of tactile sensation is probably primarily important during operations of large tumors. The robot assisted technique means an investment in expensive equipment: A robot today costs about SEK 13 million with an additional cost of SEK 11500 for single use instruments for each operation and an annual maintenance cost of SEK 900 000.

There are as yet no published studies where the different surgical techniques have been systematically compared, whether randomised prospective or simply prospective. All knowledge is at level EBM 3-4.

Despite this lack of knowledge base many are prepared to invest in the new technique. Among others Karolinska Hospital in Stockholm has acquired two robots, the University Hospital in Lund has one, as does the University Hospital in Malmö. In the USA approximately 45 % of all radical prostatectomies are carried out with robot assisted surgery. The current study has been created to evaluate this new technique in regard to oncologic and functional results, the quality of life experienced by patients and health economy aspects.

In some cases radical prostatectomy is carried out with regional lymphadenectomy. There is no consensus about which tumors or patients, defined by other means, should have the extended operation. The current situation means that indications for the extended operation including lymphadenectomy can vary between urological departments as well as between surgeons at the same department. In theory the aim of carrying out a lymphadenectomy is to improve the "oncologic result" with the unspoken implication of long term survival. There are no published studies shedding light on this problem. Local lymphadenectomy has been introduced as routine in rectal cancer surgery after a randomized study showed significantly lessened risk for local recurrence of cancer after complete lymphadenectomy [11].

2.2 Hypotesis

Robot assisted laparoscopic radical prostatectomy results in fewer lasting complications such as incontinence and impotence, but does not affect the oncologic results.

2.3 Primary aims

To compare long term morbidity in patients operated by the two techniques, as well as impaired erectile ability and incontinence.

2.4 Secondary aims

To compare the results in patients undergoing open radical prostatectomy compared to patients undergoing robot assisted laparoscopic prostatectomy regarding

1. the radicality and consequential oncologic
2. the acute complications
3. the mortality and complications associated with regional lymphadenectomy within 3 months
4. the self identified quality of life in patients
5. the health economy consequences

2.5 Study design

The intention of the study is to compare robot assisted laparoscopy with the conventional open surgery technique in regard to oncologic and functional results, self identified quality of life and cost effectiveness.

The primary study is multi-centric, prospective and not randomized.

The study also includes a randomized secondary study of a subgroup of patients with tumor stage T1-T2, Gleason-grade ≥ 7 and PSA < 15, and where the patients are randomized for radical prostatectomy with or without bilateral, regional lymphadenectomy (obturator glands).

Randomization will be stratified as to surgical technique. Operations will be carried out using robot assisted laparoscopy or with open surgery technique as described above.

Thus this study is

- an open, prospective, non-randomized study of patients who undergo radical prostatectomy either by conventional open technique or by robot assisted laparoscopy technique

- and a randomized, prospective study of the importance of regional lymphadenectomy in regard to mortality and complications within 3 months.

The "oncologic result" will be evaluated through the pathology report regarding local radicality assessed as tumor involvement in the resection margins and "PSA relapse".

This adds extra strength to the study, as it enables the possibility of a comparison of the effect of the respective techniques on mortality, measured by the surrogate variables "local radicality" and "PSA relapse". The importance of the comparison is the ability to understand the influence of confounding factors. The standardizing of the handling of the prostate gland during and after the operation and the histopathologic examination gives an improved basis for comparison. Variations in

tumor size, tumor involvement in the resection margins and Gleason grade can be actual confounding factors and standardizing the measuring of these factors makes the study stronger than other types of observational comparisons.

"PSA relapse" is defined as a renewed increase to PSA >0.5 after an initial return to zero after the operation. Laboratory measurements of PSA will be equilibrated between the laboratories analysing the samples in the study.

2.6 Inclusion criteria

1. Men with localised prostate cancer, stage T1-T2
2. No sign of remote metastases, ie stage M0
3. PSA ≤ 20
4. All Gleason grades
5. Patients otherwise judged as suitable for radical prostatectomy
6. Patients acceptance of side effects with the operation (informed consent to the operation)
7. Age ≤ 75 years
8. Absence of other cancers
9. For the randomised study of lymphadenectomy Gleason ≥ 7 and PSA < 15

2.7 Exclusion criteria pre randomising

1. BMI > 35
2. Previous cancer, though not previous basal cell cancer
3. Men with prostate cancer, stage $\geq T3$
4. The existence of remote metastases
5. PSA > 20 . Patient assessed as not suitable for laparoscopic surgery
6. Age > 75 years
7. For the randomized study of lymphadenectomy Gleason < 7 and/or PSA ≥ 15

2.8 Exclusion criterion after randomising

1. No cancer found in sample

2.9 Surgical training

All types of surgery involve training. This is particularly clear in the context of introducing new techniques or methods. The introduction of laparoscopy demonstrated this, not least regarding radical prostatectomy. There are clear indications, for example from "quality registers", that the learning curve for open radical prostatectomy is long, probably longer than for robot assisted laparoscopic prostatectomy. It is also clear that surgeons have different learning curves, independently of which technique they use. The learning period probably increases the operation time, which is well known from the introduction of laparoscopic techniques in general surgery, but there are also many indications that the clinical results from surgery are less good during the training phase. The design of the study was determined by the planning committee's assessment of the best possible model for handling these difficulties.

The departments and surgeons who initially take part in the study have extensive experience of the respective surgical techniques.

The participating departments and surgeons are required to have great collective experience and individual experience of at least 100 operations, before inclusion.

2.10 Perioperative lymphadenectomy

Patients who fulfil the following specific inclusion criteria for lymphadenectomy Gleason score ≥ 7 and PSA < 15 will be randomized for radical surgery with or without local lymphadenectomy.

Randomizing procedure to be stratified per hospital.

2.11 Randomizing procedure

Randomizing for surgery with or without lymphadenectomy is done at the Oncologic Centre, Göteborg. Contact via telephone or alternatively via OC:s home page.

2.12 Strength and statistical methods

Incontinence grade II-IV predicated in the open prostatectomy group of the study to 10%. Detection of difference in continence with variation of more than 30%, ie outside 87 - 93% can be tested with approximately 600 patients in each group.

It is intended to include 700 patients in each group of the study, i.e. per surgical technique. The aim is to start the study in 2007 and recruit patients over two years, which corresponds to surgery volumes at the participating hospitals.

The oncologic results are evaluated short term with the surrogate variable "presence of cancer in the resection margin". A difference between groups is assumed if the portion of positive margins differs by 10%. We predicate that the presence of positive margins in the open surgery group should be 20%. We therefor regard the methods as oncologically equal if the presence in the other group is within 18 - 22%. "PSA relapse" is also used as a surrogate variable for "the oncologic result" and PSA relapse is defined as a renewed increase to PSA 0.5 after initially normalizing (zero) postoperatively. A proportion of "PSA relapse" over 10% is also regarded as a difference in oncologic result. The oncologic results are evaluated per surgery technique.

The secondary study of the importance of lymphadenectomy (randomized) is designed with the intention of evaluating the methods in the short term (3 months). With results on hand regarding mortality and other complications it will be possible to decide if an extended full-scale study regarding survival is reasonable. If survival rates increase from 90% to 93% with lymphadenectomy a study requires 2720 patients to demonstrate a statistical difference ($p < 0.05$, two sided tests, statistical strength 0.8).

2.13 Strategy for inclusion and control of representation

All patients at participating departments who meet the inclusion criteria and do not display any exclusion criteria will be informed of this study and the possibility of participating. Written consent from participants is required for inclusion.

Each department will keep a log to register all patients who undergo a radical prostatectomy, making it evident if the patients meet the inclusion criteria or the reasons for their not being included in the study. The register will include those who do not meet the inclusion criteria or who must be excluded according to the protocol. Double checking will be done against the National Quality registry.

2.14 Criteria for participating hospitals

Participating hospitals will establish arrangements for the open and the robot assisted laparoscopic techniques for radical prostatectomy. Participating surgeons will have carried out at least 100 operations of the relevant kind.

2.15 Patients who accept participation in the study are registered preoperatively as per the following variables:

- Age, height and weight
- Employment
- Hereditary factors
- Other illness, medications
- Presence of abdominal hernia
- ASA class
- T-stage
- Gleason-grade in biopsies
- Number of positive biopsies
- Number of total mm cancer in diagnostic biopsies
- PSA
- IPSS-score (appendix 4:2)
- ED-score (appendix 4:3)
- Specific questionnaire – please refer to appendix 5a in the ethical application
- EuroQol (EQ-5D) – please refer to appendix 5b in the ethical application

2.16 Data collection

Clinical Record Form (CRF)

Appendix 4:1

Clinical register of hospital care

- Blood loss
- Duration of care – number of days (**2.20**)
- Need for parenteral opiates, number of days on opiates
- Mortality and complications during hospital stay
- Sick leave certification (**2.21**)
- Planned date for catheter removal
- Resource use including sick leave

Clinical registration 3 months postoperatively

- Actual number of days sick leave (**2.21**)
- Actual number of days with catheter postoperatively

- Questionnaire regarding continence and erectile function - see appendix 4:2, 4:3
- EuroQol
- PSA level
- Presence of abdominal hernia
- Health related self identified quality of life
- pT-stage
- Tumor involvement in the resection margins
- N-stage
- Gleason-score in prostate resection samples
- Mortality and complications

Clinical registration 12 months postoperatively

- Complications
- Presence of abdominal hernia
- PSA level
- Questionnaire regarding continence and erectile function
- Health related self identified quality of life

Clinical registration 24 months postoperatively

- Complications
- Presence of abdominal hernia
- PSA level
- Questionnaire regarding continence and erectile function
- Health related self identified quality of life

2.17 Participating hospitals

Sahlgrenska University Hospital, Göteborg

Carlanderska Hospital, Göteborg

Karolinska University Hospital, Solna

Additional hospitals which may participate in the study.

2.18 Criteria for preoperative investigations

Biopsy of prostate

Biopsies and surgical samples are kept according to normal patient consent in biological archive in each hospital. No specific biological archive will be established for the study.

There must be at least one series of medium size needle prostate biopsies including at least eight needles – four from each lobe - before a radical prostatectomy.

Bone scan

To be carried out on patients with Gleason-score ≥ 8 .

2.19 Surgical technique

The purpose and completed actions of each operation will be described in the attached form, appendix 3.

2.20 Duration of care

Patients will be discharged when they:

- Are fully mobilised
- Can maintain their indwelling catheter
- Are self-sufficient regarding food and drink
- Do not require parenteral pain relief

2.21 Sick leave

Sick leave is an important aspect of the degree of post-operative impact on those patients who are employed. Sick leave certification will follow the principle that the patients themselves determine their need for sick leave. The intention is to lessen the risk that expectations and/or traditions influence the length of the sick leave. Each participating department will organise sick leave approval by telephone so patients can go home with a sick leave certificate for 7 days. If further sick leave is required the patient telephones (answering service) and indicates what is needed, and a new certificate for 7 days is issued on each occasion.

2.22 Examination of samples

Examination of surgical samples will be carried out so that the following is clearly identified in the report: pT-stage, tumor involvement in the resection margins evaluated quantitatively, N-stage and Gleason-score of the excised samples.

For those randomized for lymphadenectomy the number of excised glands will be identified as to right and left side, as well as the number of glands with cancer.

2.23 Complications

Complications within 28 days will be registered and particularly

- deep vein thrombosis
- infection requiring antibiotics/other active intervention
- re-admittance to hospital regardless of reason, with diagnosis code (ICD 10)
- re-interventions by performed surgical procedures (coded according to the Swedish version of the NOMESCO Classification of Surgical Procedures Version 1.9)

2.24 Follow-up

Patients will be followed up with clinical checks, including the specific tests and examinations mentioned above, at 3 months, 12 months and 24 months after surgery. There is a specific questionnaire (appendix 4:1) for each follow-up occasion.

Follow-up via the “Cause of death registry” (at the Swedish National Board of Health and Welfare) to determine over-all survival and cancer specific survival at 10 years.

Please go to Amendments at the end of the document.

2.25 Patient’s self identified quality of life

Recording of the prevalence of symptoms, feeling of wellbeing and self identified quality of life will take place before surgery, after 3 months, 1 year and 2 years. A questionnaire will be developed for each occasion. Questions will be designed according to a concept developed by planning committee member Professor Gunnar Steineck. The concept allows for great detail and has been used 18 times for data collection, whereof three have resulted in publication in the New England Journal of Medicine. For each conceptually clean symptom information is collected regarding frequency, either individual incidence or individual prevalence, intensity and sometimes even duration. The questionnaire used in this study is based on the questionnaires, as per Steineck’s concept, developed for the randomised Swedish study which evaluated radical prostatectomy [1] and a follow-up study of open surgery and robot assisted laparoscopic prostatectomy carried out in Stockholm. A particular problem is the use of erectile aids which can affect the evaluation of sexual impotence. A specific module has been developed for erection and erection aids. There is also great detail regarding urinary leakage, pain levels in the lower abdomen and hernias. The Euroqol instrument will be used as a basis to calculate quality adjusted years of life from a health economy point of view. Each questionnaire will be tested for validity by face-to-face validity and internal loss through a preliminary study according to the protocol developed at the Unit for Clinical Cancer Epidemiology. Great importance will be placed on avoiding loss at data collection. At follow-up at three months, one year and two years a letter will first be sent to the patient, whereafter an interviewer will telephone and ask if we can send the questionnaire to those who have agreed to have it sent to their home. A thank-you and reminder letter will be sent ten days later and a reminder by telephone made after a further ten days. Possible further reminders will be decided in conjunction with the patient. This methodology which has been used 18 times for data collection has resulted in a response frequency of

85 to 92 percent for similar groups of patients. On the other hand, handing out questionnaires to patients at a clinic for prostate cancer in Stockholm resulted in a response frequency of approximately 60 percent.

2.26 Recurrence of illness

Recurrence of illness will be monitored with PSA testing during the active follow-up period. Investigation if PSA levels increase will be according to local protocol. Treatment of confirmed recurrence will be according to local protocol.

2.27 Data collection and registration

Basic documentation of care takes place in the patient log at the participating hospitals as does documentation of surgery, duration of care and follow-up. Specific clinical record forms (CRF) will be created where denoted variables are recorded in a specific database for each patient. No tape recordings or video recordings exist. Completed questionnaires and databases are saved by scanning and become primary documentation. As ten years of follow-up of survival is planned, storage for a considerable time, at least 20 years, will be at the Institute of Clinical Science. The database is saved on a computer linked to the Sahlgrenska Academy/Oncology Centre network and requires an access password. Only those directly involved in the registry and researchers have access with individual passwords.

Data will be collected regarding the situation pre surgery, events and outcomes during and immediately after surgery and during later follow-up until 24 months after surgery. After this the patient will be followed up each year at an out-patients clinic for men treated for prostate cancer for signs of recurrence and via the register for survival. A secretariat will be established to monitor that the follow-up described in the protocol takes place, reminders are sent out etc. Follow-up results from participating departments will be sent to the secretariat which is intended to be located at Sahlgrenska University Hospital in Göteborg.

The database will be based on personal ID numbers to enable follow-up of the mortality register up to ten years after surgery. The database is completely separate from existing patient logs and other hospital systems. Access is only available to authorised research staff and researchers with passwords and the database is located on a desktop computer at the Oncology Centre and linked to the University network server to safeguard the need for security with automatic backups as protection against loss of data and firewall protection against intrusion. Approval for the register (database) will be applied for from the "Privacy representative" at Sahlgrenska University Hospital, after relevant ethical approval has been received.

2.28 Ethical approval

Application for ethical approval for the study is lodged with the Ethical Approval Committee (EPN) in Göteborg.

2.29 Funding

Application for project funding has been made to the Swedish Cancer Foundation and also application for “ALF” funding from Sahlgrenska University Hospital to cover administration costs, staff and researchers. No costs for additional testing, examinations or follow-up as these conform to current practice at the participating hospitals.

Amendments

2014-06-24

Six year follow up performed as a structured telephone interview six years after surgery. Before the interview a letter will be sent to the patient informing him that the research nurse will call and that she will ask about participation in an interview.

The interview includes 14 questions, about PSA values and medication connected with recurrence of the prostate cancer. The questions have been face validated and revised before starting the follow-up.

At 6 years we plan for a retrieval of data about date and cause of death from the Swedish Cause of Death Register (National Board of Health and Welfare).

Amendments approved by Ethical committee 2014-07-28 (Dnr:277-07;T607-14) and 2015-04-24 (Dnr 277-07;T340-15).

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2014-06-24

Eight years after surgery a follow-up conducted by the same method, that is an information letter followed by a telephone call with information about the follow-up and if the patient is willing in turn followed by a questionnaire containing some 250 questions on general health, body functions, quality of life and well-being as well as recurrence of the prostate cancer. A remainder/thank you letter was sent two weeks after the questionnaire was sent out. No further remainders were made. As a basis for the questionnaire in depth, semi-structured interviews with men operated for prostate cancer about 8 years earlier were made. After analyses of the interviews, questions were put together in a first questionnaire, validated by an expert group. After revision, the questionnaire was face validated with patients and revisions were made.

At 8 years we plan for a retrieval of data about date and cause of death from the Swedish Cause of Death Register (National Board of Health and Welfare).

Amendments approved by the Ethical committee 2014-07-28 (Dnr:277-07;T607-14) and 2015-04-24 (Dnr 277-07;T340-15).

2019-05-20

Twelve years after surgery a follow-up on the lines describe for 8 years follow-up will be performed. The same methods apply, as described above. The methods used for constructing the questionnaire were those used for the 8 years questionnaire.

At 12 years we plan for a retrieval of data about date and cause of death from the Swedish Cause of Death Register (National Board of Health and Welfare).

Amendments 2020-05-25 approved by the Ethical committee 2019-07-01 (Dnr 2019-03340)

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4 APPENDICES

Appendix:

4.1 CRF preoperatively, peroperative, care duration, 3 months, 12 months and 24 months postoperatively

4.2 ED-score

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4 APPENDICES 17

1. ORGANISATION

1.1 Planning committee:

Bo Anderberg, Professor, Karolinska Institute

Ingela Björholt, PhD, Sahlgrenska Akademin

Jan-Erik Damber, Professor, Sahlgrenska Akademin

Eva Haglind, Professor, Sahlgrenska University Hospital/ Sahlgrenska Academy

Jonas Hugosson, Professor, Sahlgrenska University Hospital/Sahlgrenska Academy

Elisabet Lindholm, ML, Sahlgrenska University Hospital

Gunnar Steineck, Professor, Oncology Centre/ Sahlgrenska University Hospital /Sahlgrenska Academy

Peter Wiklund, Professor, Karolinska Institute

Thordis Thorsteinsdottir, RN, PhD student, Oncology Centre/Göteborg

The committee started working in 2005 and is responsible for the design of the protocol

1.2 Principal investigator:

Eva Haglind

1.3 Deputy principal investigator:

Gunnar Steineck

1.4 Study secretariat:

Sahlgrenska University Hospital, Göteborg. Research nurse Ingrid Höglund-Karlsson, RN.

1.5 Study steering committee:

Planning committee, the research nurse Ingrid Höglund-Karlsson, RN, Sahlgrenska University Hospital and the local investigators at each participating department of Urology.

”Post.docs” in the study are Johan Stranne, MD and Stefan Carlsson, MD.

Local investigators are: Johan Stranne, Sahlgrenska University Hospital, Göteborg; Jonas Hugosson, Carlanderska sjukhuset, Göteborg; Erik Pileblad, Lundby sjukhus, Göteborg; Mikael Lagerkvist, UroClinic, StGörans sjukhus, Stockholm; Thomas Jiborn, University Hospital UMAS, Malmö; Stefan Carlsson, Karolinska University Hospital/Solna, Solna, Christer Edlund, Kungsbacka hospital, Ulrika Westlund, Södersjukhuset, Stockholm, Ola Bratt, Helsingborg hospital, Hans Boman, Alingsås hospital.

The committee meets at least twice per year and whenever a committee member indicates that a meeting is necessary.

1.6 Monitoring:

Responsibility: Eva Haglind via research nurse Ingrid Höglund-Karlsson.

Ongoing follow-up and control of data collection as well as adherence to the protocol through communication with the respective local investigators. Visits to the participating hospitals is planned on a yearly basis.

The study secretariat is in charge of the logistics for send out of questionnaires at 3, 12 and 24 months, including remainders.

1.7 Writing committee, access to data, timing of comparative analysis, publications:

Writing committee: steering committee incl. local investigators from departments joining the study later on and active researchers involved in the principal study or part thereof.

Access to data: Local investigator at each participating department may have access to data for patients included at that department during the run of the study. Such data could be part of local quality assurance and in publications about that department only.

Timing of comparative analysis: Only the study design and level of inclusion can be presented during the ongoing study. No results will be analysed during the study. No partial results with comparisons between the study groups will be published. The steering committee decides about analysis of data as well as timing of this. The steering committee will discuss and decide on the conclusions from the results. The steering committee decides about co-authorship using customary, international protocol. The steering committee decides on publication of the results.

Publication: The primary and secondary aims with comparisons between the groups as described in this protocol will be analyzed after the inclusion and follow-up in accordance with the protocol. Publication refers to international peer reviewed scientific journals. The steering committee will decide if reporting at relevant international conferences takes place and by whom.

Customary protocol regarding co-authorship will be observed.

2 PROTOCOL

2.1 Background

Diagnosis of early prostate cancer has increased noticeably during the last 10 years and this has resulted in more men being offered curative treatment. The number of radical prostatectomies in Sweden has increased from a couple of hundred to more

than two thousand per year. This number will probably increase further over the next five years.

The only randomised study so far, SPCG-4, showed a significant difference in mortality at follow-up after 8.2 years. The mortality rate from prostate cancer was 14.4 percent in the control group who had no surgery but who were followed actively ("watchful waiting"), and 8.6 percent in the group who had radical prostatectomy, analysed as "intention to treat" [1]. Mortality, independantly of the cause, changed from 32 percent to 27 percent [1]. Thus the absolute effect of surgery is 5 percent both for deaths from prostate cancer and total mortality and twenty men must have surgery to prevent the early death of one. This figure includes a large proportion, close to three quarters, of the men who were diagnosed with prostate cancer when they sought help regarding problems with micturation. These days when many men are diagnosed without micturation problems but after health checks for Prostate Specific Antigen (PSA) in the blood, the number is certainly higher, i.e. more than twenty men must have surgery to save one man from premature death. The knowledge that radical surgery of prostate cancer improves survival, has resulted in surgery becoming the most common form of treatment for early prostate cancer, not only in Sweden but in most countries. A very rough estimate indicates that two million men world-wide have had a radical prostatectomy, despite the cited study showing large numbers of patients experiencing ongoing complications. A comparative study is currently being done in the USA and a study in England includes surgery, radiation treatment and active monitoring. The oncological results from these studies will not be available for 5-10 years.

The treatment aims to radically remove the tumor and thus increase the proportion of patients surviving 10 years without recurrence, the "oncologic result". Good surgical technique means that the proportion of patients where the tumor is totally excised ("radical surgery") must be high, or the primary aim of the operation is jeopardized. At the same time the technique must be as "atraumatic" as possible to minimize the risk for complications. The most serious impairments for the patient are incontinence and impotence. Increased experience has improved surgical technique and the risk of such damage has decreased. The number of patients with lasting impotence and/or incontinence after the operation is still high. The risk of developing an inguinal hernia after open radical prostatectomy is reported to be higher than expected [2].

Based on the expected survival effects and remaining life expectancy in different age cohorts, the radical operation is these days offered to patients with tumors limited to the prostate gland ("early tumors") and who have a long life expectancy, often with an upper age limit of 70 years. The aim is to carry out surgery with a short stay in hospital, a short recovery period and low risk of subsequent illness. This ameliorates patient suffering and lessens the cost to individuals and to society.

Unpublished data from the study shows that with adjustment for the number of symptoms "watchful waiting" decreases quality of life, indicating that the diagnosis in itself causes psychological damage (1). There is a clear link between the number of symptoms and self identified quality of life and also between the number of symptoms and a feeling of wellbeing. The nearly linear correlation indicates that a decrease in the portion of men with sexual impotence or urinary leakage after surgery will improve their self identified quality of life and

wellbeing. Unpublished data also shows that the quality of life decreases dramatically for castrated men in the group under "watchful waiting" but not for the men in the group who had a radical prostatectomy.

Approximately 10 years ago it was suggested that laparoscopy would result in better results than the open surgical technique. This was based on the possibility that the laparoscopic technique means better lighting, improved enlargement and makes it possible for the entire surgical team to follow the operation. It also means that the operation is carried out with instruments in the cramped space inside the lower pelvis. A laparoscopic technique was developed and adopted in a small number of urological centres round the world. Reports have described long operations and long training times for surgeons [3, 4]. There are also reports of decreased numbers of complications. There are no prospective, comparative or randomised studies, and the level of knowledge does not allow any conclusions to be drawn. There are no reports of long term outcomes. The technical difficulties have prevented the technique being widely used.

Robot assisted laparoscopy technique has been used for some years to carry out radical prostatectomies. The use of this technique retains all the theoretical advantages of laparoscopy with the addition of three-dimensional images and more degrees of freedom in the use of the instruments. In theory this should be an advantage, not least while working inside the lower pelvis, where there is always a lack of space particularly in males. The published results from individual surgeons and departments point to possibly fewer complications than the published results of open surgery [5-7]. There are no evaluations of this technique in randomised or prospective comparative studies. Despite this the robot assisted technique is increasingly being used for radical prostatectomies, according to promising preliminary reports, both regarding the number of patients with impotence/incontinence and the portion of patients where radicality has been achieved [8, 9]. Compared to laparoscopy the robot assisted laparoscopy technique means a shorter learning period and also shorter surgery times compared to classic laparoscopy [10]. The published reports also indicate the possibility of decreased bleeding during surgery and shorter hospital stays [6].

As well as the advantages described above there are possible disadvantages, which have not been scientifically evaluated. The technique is only about five years old and potential technique specific complications are completely unknown. The robot does not produce so called "haptic feedback" which means that tactile sensation is lost. The value of tactile sensation is probably primarily important during operations of large tumors. The robot assisted technique means an investment in expensive equipment: A robot today costs about SEK 13 million with an additional cost of SEK 11500 for single use instruments for each operation and an annual maintenance cost of SEK 900 000.

There are as yet no published studies where the different surgical techniques have been systematically compared, whether randomised prospective or simply prospective. All knowledge is at level EBM 3-4.

Despite this lack of knowledge base many are prepared to invest in the new technique. Among others Karolinska Hospital in Stockholm has acquired two robots, the University Hospital in Lund has one, University Hospital in Malmö has one and there is one in the Swedish Western Region in Sahlgrenska University Hospital. In the USA approximately 45 % of all radical prostatectomies are carried

out with robot assisted surgery. The current study has been created to evaluate this new technique in regard to oncologic and functional results, the quality of life experienced by patients and health economy aspects.

In some cases radical prostatectomy is carried out with regional lymphadenectomy. There is no consensus about which tumors or patients, defined by other means, should have the extended operation. The current situation means that indications for the extended operation including lymphadenectomy can vary between urological departments as well as between surgeons at the same department. In theory the aim of carrying out a lymphadenectomy is to improve the "oncologic result" with the unspoken implication of long term survival. There are no published studies shedding light on this problem. Local lymphadenectomy has been introduced as routine in rectal cancer surgery after a randomized study showed significantly lessened risk for local recurrence of cancer after complete lymphadenectomy [11].

2.2 Hypotesis

Robot assisted laparoscopic radical prostatectomy results in fewer lasting complications such as incontinence and impotence, but does not affect the oncologic results.

2.3 Primary aim

To compare long term morbidity in patients operated by the two techniques, primarily incontinence 12 months postoperatively.

2.4 Secondary aims

To compare the results in patients undergoing open radical prostatectomy compared to patients undergoing robot assisted laparoscopical prostatectomy regarding

6. dysfunction regarding erection at 12 and 24 months as well as incontinence 24 months postoperatively
7. the radicality and consequential oncologic result
8. the acute complications
9. the self identified quality of life in patients
10. the health economy consequences

2.5 Study design

The intention of the study is to compare robot assisted laparoscopy with the conventional open surgery technique in regard to oncologic and functional results, self identified quality of life and cost effectiveness.

The study is multi-centric, prospective and not randomized.

Thus this study is thus

- an open, prospective, non-randomized study of patients who undergo radical prostatectomy either by conventional open technique or by robot assisted laparoscopic technique. An interim analysis was performed by an external monitoring committee (2.11) in December 2009 regarding primary end-point

results in all patients followed up at that stage (2010-12-01). The committee was asked to use the results (not known by anyone person participating in the study) as basis for a recommendation about the inclusion numbers. The steering committee of LAPPRO has decided (2010-03-12) to accept the recommendation by the monitoring committee to perform the study as a 2:1 (robot assisted:open) model for the inclusion numbers.

The "oncologic result" will be evaluated through the pathology report regarding local radicality assessed as tumor involvement in the resection margins and "PSA relapse" defined as PSA value >0.2 at two separate occasions after an initial postoperative decrease to <0.1 (not possible to determine). Patients without the expected decrease to <0.1 after the operation will be followed according to this protocol but will be analyzed as a sub-population.

This adds extra strength to the study, as it enables the possibility of a comparison of the effect of the respective techniques on mortality, measured by the surrogate variables "local radicality" and "PSA relapse". The importance of the comparison is the ability to understand the influence of confounding factors. The standardizing of the handling of the prostate gland during and after the operation and the histopathologic examination gives an improved basis for comparison. Variations in tumor size, tumor involvement in the resection margins and Gleason grade can be actual confounding factors and standardizing the measuring of these factors makes the study stronger than other types of observational comparisons.

2.6 Inclusion criteria

10. Men with localised prostate cancer, stage T1-T3
11. No sign of remote metastases, ie stage M0
12. PSA ≤ 20
13. All Gleason grades
14. Patients otherwise judged as suitable for radical prostatectomy
15. Patients' acceptance of side effects with the operation (informed consent to the operation)
16. Age ≤ 75 years
17. Absence of other cancers

2.7 Exclusion criteria pre operatively

8. BMI >35
9. Previous cancer, though not previous basal cell cancer
10. Men with prostate cancer, stage $\geq T3$
11. The existence of remote metastases
12. PSA >20 .
13. Patient assessed as not suitable for laparoscopic surgery
14. Age >75 years

2.8 Surgical training

All types of surgery involve training. This is particularly clear in the context of introducing new techniques or methods. The introduction of laparoscopy demonstrated this, not least regarding radical prostatectomy. There are clear indications, for example from "quality registers", that the learning curve for open radical prostatectomy is long, probably longer than for robot assisted laparoscopic prostatectomy. It is also clear that surgeons have different learning curves, independently of which technique they use. The learning period probably increases the operation time, which is well known from the introduction of laparoscopic techniques in general surgery, but there are also many indications that the clinical results from surgery are less good during the training phase. The design of the study was determined by the planning committee's assessment of the best possible model for handling these difficulties.

The departments and surgeons participating in the study should have extensive experience and on an individual level an experience of >100 operations, before start of inclusion. Surgeons in training can perform part of or alternatively an entire operative procedure with the assistance of an accredited (>100 operations) surgeon. The patients where the operation fulfills these criteria can be included and data collected. In the analyses of data the patients operated as described above will be analyzed as a sub-population. The primary analysis will concern the 700+700 patients, who were operated by accredited (>100 operations) surgeons.

2.9 Inclusion and registration

Registration of included patients is by telephone call to Oncology Centre, Göteborg at 031-3439070 8am – 16 pm, weekdays. A list of included patients is sent to the local investigator at each participating department (own patients) and to the Study secretariat (all patients).

2.10 Strength and statistical methods

Incontinence grade II-IV predicated in the open prostatectomy group of the study to 10%. Detection of difference in continence which differs by more than 30 relative percent, i.e. outside 87 - 93% can be tested with approximately 600 patients in each group. (Alfa=0.05, statistical power at 80%).

New version 10 03 25

The recommendation about inclusion numbers made by the external monitoring committee (December 2009) is based on the possibility to with Alfa=0.05, statistical power 80% and a two tailed test be able to show a difference of 5%, using the basic incontinence rate in the open group is between 10 and 18%. To reach this 600 patients are needed in the open group and 1200 in the robot assisted laparoscopic group and with a margin for individuals not possible to use for evaluation, the group recommends 700 + 1400 patients as accrual aim. The steering committee decided in session (2012-03-12) to accept the recommendation, and the study therefore aims for an inclusion of 700 + 1400 patients possible to evaluate in the primary analysis, i.e. operated by surgeons with experience from more than 100 procedures. The committee further decided to submit an amendment to the Ethical board and to the registration in ISRCTN.

~~It is intended to include 700 patients operated by open technique and about 1000 patients operated by robot assisted laparoscopic technique in each group of the study, i.e. per surgical technique, all of which operated by accredited surgeons and also the patients operated by surgeons under training in participating departments. The aim is to start the study in 2007 and recruit patients over two years, which corresponds to surgery volumes at the participating hospitals.~~

At the planning of the study the department with the largest number of open operations was Sahlgrenska University Hospital. When The Swedish Western Region acquired a da Vinci robot for research and development, we found that this was immediately used for robot assisted laparoscopic prostatectomy procedures. Due to this the planning was no longer accurate regarding the possible number of open prostatectomies. A number of departments performing open prostatectomy has joined the study, resulting in a certain difference in inclusion rate. Thus the number of included robot assisted prostatectomies will be larger, as can be seen in the planning above. The aim is to stop inclusion when the open arm has accrued 700 patients, estimated to occur around October 2010.

The oncologic results are evaluated short term with the surrogate variable “presence of cancer in the resection margin”. A difference between groups is assumed if the portion of positive margins differs by 10%. We predicate that the presence of positive margins in the open surgery group should be 20%. We therefor regard the methods as oncologically equal if the presence in the other group is within 18 - 22%. ”PSA relapse” is also used as a surrogate variable for ”the oncologic result” and PSA relapse is defined as a renewed increase to PSA 0.5 after initially normalizing (zero) postoperatively. A proportion of ”PSA relapse” over 10% is also regarded as a difference in oncologic result. The oncologic results are evaluated per surgery technique.

2.11 Interim analysis and external monitoring committee

A monitoring committee of three external scientists, not in any sense involved in the study, will perform an interim analysis, when 500 patients have been included in each group. The aim is to suggest if the result regarding the primary end-point is in line with the numbers used in the power calculation on which the inclusion number is based or if the inclusion number should be enlarged. The Steering committee decides about the continued inclusion.

2.12 Strategy for inclusion and control of representation

All patients at participating departments who meet the inclusion criteria and do not display any exclusion criteria will be informed of this study and the possibility of participating. Written consent from participants is required for inclusion.

Each department will keep a log to register all patients with early prostate cancer. In this log is noted if the patient fulfills the inclusion criteria (2.6) and for non-included patients, the reason for non-inclusion.

All included patients are registered at Oncology Centre, Göteborg as described under 2.9.

The study secretariat runs a registry that will include those who do not meet the inclusion criteria (2.6) or who must be excluded according to the protocol (2.7). Double checking will be done against the National Quality registry.

2.13 Criteria for participating hospitals

Participating hospitals will establish arrangements for the open and the robot assisted laparoscopic techniques respectively, for radical prostatectomy. Participating surgeons will have carried out at least 100 operations of the relevant kind.

2.14 Patients who accept participation in the study are registered preoperatively as per the following variables:

- Age, height and weight
- Employment
- Hereditary factors
- Other illness, medications
- Presence of abdominal hernia
- ASA class
- T-stage
- Gleason-grade in biopsies
- Number of positive biopsies
- Number of total mm cancer in diagnostic biopsies
- PSA
- IPSS-score (appendix 4:2)
- ED-score (appendix 4:3)
- Health and well-being in connection with prostate surgery, questionnaire (appendix 4.2) including among others
 - IPSS score (continence)
 - ED score (potency)
 - EuroQol (EQ-5D) –(Health Related Patient Experienced Quality of Life)

2.15 Data collection

Clinical Record Form (CRF) Appendix 4:1 as well as questionnaires Appendix 4.2

Clinical register of hospital care

- Blood loss
- Duration of care – number of days (**2.20**)
- Need for parenteral opiates, number of days on opiates
- Mortality and complications during hospital stay
- Sick leave certification (**2.21**)
- Planned date for catheter removal
- Resource use including sick leave

Clinical registration 3 months postoperatively

- Actual number of days sick leave (**2.21**)
- Actual number of days with catheter postoperatively
- Health and well-being in connection with prostate surgery, questionnaire (appendix 4.2) including among others
 - IPSS score (continence)
 - ED score (potency)
 - EuroQol (EQ-5D) –(Health Related Patient Experienced Quality of Life)
- PSA level
- Presence of abdominal hernia
- Health related self identified quality of life
- pT-stage
- Tumor involvement in the resection margins
- N-stage
- Gleason-score in prostate resection samples
- Mortality and complications

Clinical registration 12 months postoperatively

- Complications
- Presence of abdominal hernia
- PSA level
- Health and well-being in connection with prostate surgery, questionnaire (appendix 4.2) including among others
 - IPSS score (continence)
 - ED score (potency)
 - EuroQol (EQ-5D) –(Health Related Patient Experienced Quality of Life)

Clinical registration 24 months postoperatively

- Complications
- Presence of abdominal hernia
- PSA level
- Health and well-being in connection with prostate surgery, questionnaire (appendix 4.2) including among others
 - IPSS score (continence)
 - ED score (potency)
 - EuroQol (EQ-5D) –(Health Related Patient Experienced Quality of Life)

2.16 Participating hospitals

Sahlgrenska University Hospital, Göteborg

Carlanderska Hospital, Göteborg

Karolinska University Hospital, Solna

Lundby hospital, Göteborg

University Hospital, UMAS, Malmö

UroClinic, S:t Görans Hospital, Stockholm

Urology section, Department of Surgery, Uddevalla hospital

Urology, Södersjukhuset, Stockholm

Urology, Department of Surgery, Varberg/Kungsbacka hospital, Varberg

Alingsås hospital

Helsingborg hospital

Additional hospitals which may participate in the study.

2.17 Criteria for preoperative investigations

Biopsy of the prostate gland

Biopsies and surgical samples are kept according to normal patient consent in biological archive in each hospital. No specific biological archive will be established for the study.

There must be at least one series of medium size needle prostate biopsies including at least eight needles – four from each lobe - before a radical prostatectomy.

Bone scan

To be carried out on patients with Gleason-score ≥ 8 .

2.18 Surgical technique

The purpose and completed actions of each operation will be described in the attached form, CRF Appendix 4.1.

2.19 Duration of care

Patients will be discharged when they:

- Are fully mobilised
- Can maintain their indwelling catheter
- Are self-sufficient regarding food and drink
- Do not require parenteral pain relief

2.20 Sick leave

Sick leave is an important aspect of the degree of post-operative impact on those patients who are employed. Sick leave certification will follow the principle that the patients themselves determine their need for sick leave. The intention is to

lessen the risk that expectations and/or traditions influence the length of the sick leave.

The patient will leave the hospital with a sick leave certificate of 14 days.

Each participating department will organise sick leave approval by telephone. If further sick leave is required the patient telephones (answering service) and indicates his need. The sick leave will then be prolonged by certificate for 7 days issued on each occasion until a total of 6 weeks. If the patient needs more than 6 weeks sick leave a visit to the treating urologist will be arranged, in order to follow-up progress and complications postoperatively.

It is important that the routine for sick leave handling is described in some detail in the “Patient information”, in order to clarify for the patient that this routine is part of the study protocol. At discharge the patient should receive written information about the sick leave routines including accurate telephone numbers to be used if a need for extended sick leave is at hand.

2.21 Examination of specimen

Examination of surgical samples will be carried out so that the following is clearly identified in the report: pT-stage, tumor involvement in the resection margins evaluated quantitatively, N-stage and Gleason-score of the excised samples.

Routines for the handling of the specimen, for the examination and the pathology report and are described in a report by Drs Fredrik Pettersson and Carl-Gustav Pihl in collaboration with psot.doc. Stefan Carlsson and are included as minutes together with the underlying documents (Appendix 4.3). All participating centres must follow these guidelines for examination of specimen.

The tumor volume is a measure of quality and can differ between departments. This can be measured later, if the specimen were handled according to the guidelines.

After finalizing the inclusion the aim is to re-examine all specimen glasses by an external pathologist, who is not participating in the study. This would mean an amount of work which could be difficult to manage, due to the scarcity of pathologists in Sweden. Due to this an external re-examination of a random sample of specimens from all participating departments will take place during the study. If this analysis should reveal differences between participating departments further consideration can take place, with the aim to reach a decision about a final re-examination of all specimens. If a re-examination of all specimens is performed the result of this should be the final result regarding the pathology report of the specimens. The extent of this re-examination will be decided in relation to the financing of the study, and the PI has the final decision, as responsible for the economy of the study.

2.22 Complications

Complications within 28 days will be registered and particularly

- deep vein thrombosis

- infection requiring antibiotics/other active intervention
- re-admittance to hospital regardless of reason, with diagnosis code (ICD 10)
- re-interventions by performed surgical procedures (coded according to the Swedish version of the NOMESCO Classification of Surgical Procedures Version 1·9)

2.23 Follow-up

Patients will be followed up with clinical checks, including the specific tests and examinations mentioned above, at 3 months (6-12 weeks), 12 months and 24 months after surgery. There is a specific questionnaire (appendix 4:1) for each follow-up occasion.

Follow-up via the “Cause of death registry” (at the Swedish National Board of Health and Welfare) to determine over-all survival and cancer specific survival at 10 years.

2.24 Patient’s self identified quality of life

Recording of the prevalence of symptoms, feeling of wellbeing and self identified quality of life will take place before surgery, after 3 months, 1 year and 2 years. A questionnaire will be developed for each occasion. Questions will be designed according to a concept developed by planning committee member Professor Gunnar Steineck. The concept allows for great detail and has been used 18 times for data collection, whereof three have resulted in publication in the New England Journal of Medicine. For each conceptually clean symptom information is collected regarding frequency, either individual incidence or individual prevalence, intensity and sometimes even duration. The questionnaire used in this study is based on the questionnaires, as per Steineck’s concept, developed for the randomised Swedish study which evaluated radical prostatectomy [1] and a follow-up study of open surgery and robot assisted laparoscopic prostatectomy carried out in Stockholm. A particular problem is the use of erectile aids which can affect the evaluation of sexual impotence. A specific module has been developed for erection and erection aids. There is also great detail regarding urinary leakage, pain levels in the lower abdomen and hernias. The Euroqol instrument will be used as a basis to calculate quality adjusted years of life from a health economy point of view. Each questionnaire will be tested for validity by face-to-face validity and internal loss through a preliminary study according to the protocol developed at the Unit for Clinical Cancer Epidemiology. Great importance will be placed on avoiding loss at data collection. At follow-up at three months, one year and two years a letter will first be sent to the patient, whereafter an interviewer will telephone and ask if we can send the questionnaire to those who have agreed to have it sent to their home. A thank-you and reminder letter will be sent ten days later and a reminder by telephone made after a further ten days. Possible further reminders will be decided in conjunction with the patient. This methodology which has been used 18 times for data collection has resulted in a response frequency of 85 to 92 percent for similar groups of patients. On the other hand, handing out questionnaires to patients at a clinic for prostate cancer in Stockholm resulted in a response frequency of approximately 60 percent.

Each participating department will have a routine for hand-out and collection of the peroperative questionnaire. The department is responsible for sending these questionnaires as well as all CRFs without delay to Oncology Centre, Göteborg for

registration in the data base. The questionnaires at 3, 12 and 24 months follow-up (see above) are sent out from the study secretariate directly to the patient, after a letter and a telephone call in which the patient consents.

2.25 Recurrence of illness

Recurrence of illness will be monitored with PSA testing during the active follow-up period. Recurrence is defined as follows: PSA returned to levels above the detection level at each laboratory. Investigation if PSA levels increase will be according to local protocol. Treatment of confirmed recurrence will be according to local protocol.

2.26 Data collection and registration

Basic documentation of care takes place in the patient log at the participating hospitals as does documentation of surgery, duration of care and follow-up. Specific clinical record forms (CRF) will be created where denoted variables are recorded in a specific database for each patient. No tape recordings or video recordings exist. Completed questionnaires and databases are saved by scanning and become primary documentation. As ten years of follow-up of survival is planned, storage is planned for a considerable time, at least 20 years. Data is registred in the database, which will be in a computer in the Göteborg University network at Oncology Centre, Göteborg. The network and the database requires an access password. Only those directly involved in the registry of data and researchers have access with individual passwords. If datasets are to be copied from the database and at analysis of data, a joint decision by the PI and the dep. PI is required.

Data will be collected regarding the situation pre surgery, events and outcomes during and immediately after surgery and during later follow-up until 24 months after surgery. After this the patient will be followed up each year at an out-patients clinic for men treated for prostate cancer for signs of recurrence and via a national registry (“Cause of death”) for survival.

A secretariat will be established to monitor the study, assist at initiation in departments joining the study as well as during the inclusion period. The secretariat will organize and run the contact with and send out tooof questionnaires to the patients. The secretariat is located at Sahlgrenska University Hospital in Göteborg.

In parallell to this study the participating departments are part of the established “National quality registry for prostate cancer”. As of 2008 this registry will include ED score and IPSS score and some questions about self eported quality of life. These questionnaires are administred by the quality registry. LAPPRO and the quality registry will on both sides in the letters to the patients inform that similar questions are asked by both parties, before and 3 months after the operation.

The database will be based on personal ID numbers to enable follow-up of the mortality register up to ten years after surgery. The database is completely separate from existing patient logs and other hospital systems. Access is only available to authorised research staff and researchers with passwords. The database is located on a desktop computer at the Oncology Centre, Göteborg and linked to the

University network server to safeguard the need for security with automatic backups as protection against loss of data and firewall protection against intrusion.

2.27 Health economy

The health economic analysis will be based on experience from randomized trials of laparoscopy for the treatment of colonic cancer (COLOR) and rectal cancer (COLOR II) (12,13). The resource consumption data will be part of the CRFs for the operation, the hospital stay and the follow up during 24 months. Quality of life is part of the data, in the specific questionnaire and in EuroQol, the latter in order to enable us to calculate the traditional index “quality adjusted years of life”. No health economy analysis will be made for any participating department. The analysis will be made after the active follow-up period is at an end, for the entire population and only with the aim to compare the two surgical techniques. A validation of data of importance for the health economic analysis is planned to take place after the first 200 patients have been included.

2.28 Ethical approval

Application for ethical approval has been granted by the Ethical Approval Committee (EPN) in Göteborg 2007-01-19 Dnr 277-07.

Approval for the register (database) from the “Privacy representative” at Sahlgrenska University Hospital was given (number 29280).

2.29 Funding

Grants from the Swedish Cancerfoundation (Eva Haglind) och ALF, Sahlgrenska Universitetssjukhuset (Eva Haglind) as well as from the Swedish Western region/FK (Eva Haglind) has been approved and will be used to cover administration costs, staff and researchers. No costs for additional testing, examinations or follow-up as these conform to current practice at the participating hospitals.

2.30 Start of inclusion

The start of inclusion was by September 1, 2008.

3 REFERENCES

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4 APPENDICES

Appendix:

4.1 CRF preoperatively, peroperative, care duration, 3 months, 12 months and 24 months postoperatively

4.2 ED-score