

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Bill-Axelsson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* 2005;352:1977-84.

SPCG-4

**EXPECTANT MANAGEMENT OR
RADICAL PROSTATECTOMY
FOR EARLY PROSTATIC CANCER
(T0d-T2, NX, MO,G1-2)**

A multicentre study

Scandinavian Prostatic Cancer Group

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Note:

Amendments made during the course of the study are in *bold italics*

FLOW CHART SPCG-4

See protocol:

Newly diagnosed T0d - T2 (digital rectal palpation, transurethral resection)		
High/intermediate differentiation		
Age < 75 years (≤ 70) Life expectancy not substantially reduced (follow-up possible)		5.3.1 - 5.3.7
Surgical risk not clearly increased		
+		
No metastases at chest radiography or bone scan (+ no sign of upper urinary tract stasis)		5.3.8
S-PAP < 150%, or PSA < 50		
≤ 4 months from diagnosis		
Randomisation, tel. 018-664543		
Expectant management	Prostatectomy	
Special information	Special information	16.3, 16.4
	Radical operation < 2 months after randomisation	7.2
Follow-up according to protocol - 6, 12, 18, 24 months - then yearly for at least 8 years		8., 9.

1. SUMMARY

Radical prostatectomy is becoming routine treatment for localised prostatic cancer, the aim being to reduce the death rate by early local control of the disease. If the operation can achieve this reduction, the case for early diagnosis by screening is strengthened. Until such effect has been documented, however, the method should be regarded as experimental.

One of the main problems in assessing the value of radical prostatectomy is the strict selection of cases in which the operation is used. It has been demonstrated that even without treatment the disease has a favourable natural course, and the mortality from this cancer is low.

Against this background, the Scandinavian Prostatic Cancer Group (SPCG) considered exhaustive documentation of the advantages and possible drawbacks of radical prostatectomy to be essential. It will be made within the framework of a prospective multicentre study in the form of a randomised trial, in which radical prostatectomy is compared with primary expectant management. The study is based on the following protocol, evolved - in consultation with SPCG and all participating centres - by Hans-Olov Adami, Jan-Erik Johansson, Lars Holmberg and Bo Johan Norlén.

2. PARTICIPATING CENTRES AND INVESTIGATORS

- 2.1 The study is open to all urology departments subject to the following criteria:
 - The protocol shall be accepted by responsible urologists.
 - The local organisation should permit consideration for recruitment to the study of all consecutively diagnosed patients who satisfy the criteria for inclusion.
- 2.2 The study shall remain open to participation until the number of participant centres is judged to be sufficient.
- 2.3 To maintain high quality, the expected number of randomisable patients in each centre should be at least five per year. If a centre randomises fewer than five patients during two consecutive years, that centre should be excluded from the study.
- 2.4 A register of participating centres shall be kept, and continuously updated, at the study's secretariat.

3. BACKGROUND AND MOTIVATION

3.1 Incidence and survival

In Sweden 4 370 cases of prostatic cancer were diagnosed in 1984. The patients' mean age at diagnosis was 71 years. The age-standardised incidence of prostatic cancer had risen by 39% in the preceding 20 years¹, but the mortality had only insignificantly increased². Increased diagnostic activity, improved methods of diagnosis and true rise in incidence probably all were contributory factors. The number of tumours detected at an early stage has therefore increased. The five-year survival rates in two Swedish studies comprising all stages of prostatic cancer were 31%³ and 35%⁴. Metastases are present at diagnosis in 25-50% of cases. The prognosis then is poor, with five-year survival only 15-25%^{3,5}. In a study from Örebro, localised forms of prostatic cancer comprised 43% of all newly detected cases⁶. Such patients have a considerably more favourable prognosis, and most deaths are due to intercurrent disease.

3.2 Natural course of early prostatic cancer

The natural history of localised prostatic cancer stages previously was not adequately charted. Some more recent Nordic studies showed progression in up to 50% of cases during five-year follow-up⁷⁻⁹. These series were small and selected, and no survival curves were presented. The Örebro study⁶, in which early prostatic cancer received no primary treatment, clarified the natural course of these early tumours⁶. The series comprised 223 of 227 consecutively diagnosed cases. The progression-free survival after five years (with 95% confidence interval) was 71.8 (65.5-78.1)%, and survival corrected for deaths from other causes than prostatic cancer was 93.8 % (88.3-97.6)%. Neither age at diagnosis nor size of tumour had prognostic significance, but differentiation grade was strongly correlated to risk of death from prostatic cancer.

3.3 Untreated control group

Although 10-30% of the patients in the Örebro series⁶ probably had lymph-node metastases¹⁰ and nine of the patients had poorly differentiated tumours, the mortality from prostatic cancer was low in patients with primary expectant management. This indicates that intendedly curative measures not shown to influence mortality in early prostatic cancer, viz. radical prostatectomy, full-dose radiotherapy, interstitial irradiation or neodymium-YAG-laser, should be compared with primarily untreated controls in randomised trials. The main purpose is to study mortality from prostatic cancer. Other important measures of effect are progression-free survival, quality of life and care requirements.

Although it would be desirable to limit comparative studies to patients free from lymph-node metastases, this would require evacuation of the regional nodes, the only reliable method for classification of lymph-node status.

The patients thereafter randomised to primary expectant management, this operation would then have been performed without influencing therapy, which is ethically dubious. An alternative is to enrol patients without knowledge of lymph-node status and limit lymphadenectomy to those who are randomised to and accept intendedly curative treatment, i.e. radical prostatectomy.

3.4 Radical local treatment

In other countries, especially in the USA, localised prostatic cancer has for many years been treated with **radical prostatectomy**¹¹. Refinements of surgical technique have reduced the postoperative morbidity. The risk of incontinence is small and in many cases potency can be preserved¹¹. The surgical mortality in various series ranges from 0 to 1.7%¹¹. In general, local tumour control is achieved with radical prostatectomy. Metastases, however, develop in up to 30% of the patients¹¹⁻¹³, with high risk of death from prostatic cancer. Five-year survival varies from 75 to 90%¹¹⁻¹⁴. In a comparison between radical prostatectomy and placebo for localised prostatic cancer, with c. 30 assessable cases in each arm of the study, the Veterans Administration Urological Research Group (VA-group) found no clear difference between the two methods¹⁵. This study has been criticised as being inadequately evaluated and with few patients. There was also relatively large dropout.

In another randomised study (Uro-Oncology Research Group), radical prostatectomy was compared with full-dose **radiotherapy** for localised prostatic cancer¹⁶. The results were somewhat better with surgery than with radiotherapy as regards progression-free survival. That report and non-randomised studies of curative treatment for localised prostatic cancer¹⁷ indicated that surgery probably offers better local control of the disease than various (external or internal) radiotherapy options.

3.5 Adjuvant treatment

Hormonal therapy has long been given as preoperative or postoperative adjuvant in prostatic cancer. At the Mayo Clinic, orchidectomy has been used as postoperative hormonal treatment in patients with lymph-node metastases¹⁸. Progression-free survival^{18,19} and total survival¹⁹ were longer than in patients without postoperative orchidectomy. The patients were not randomised, however, the decision for or against orchidectomy being made by the surgeon.

Chemotherapy as cyclophosphamide or estramustine has been used as long-term adjuvant chemotherapy after radical prostatectomy²⁰, but preliminary evaluation showed no significant difference in remission time between these two groups or in comparison with patients without adjuvant chemotherapy.

Local radiotherapy as adjuvant following radical prostatectomy^{21,22} can reduce the incidence of local recurrence of prostatic cancer compared with non-irradiated patients, but does not influence the risk of distant metastasis.

3.6 Nordic custom

In the Nordic countries, patients with localised prostatic cancer of high or intermediate differentiation grade previously were often given no primary treatment. In 1982 an inquiry conducted by SPCG (Scandinavian Prostatic Cancer Group) showed that most Nordic urologists employed a "watchful waiting" strategy for early stages of prostate cancer. As a consequence of improved surgical technique, however, radical prostatectomy is increasingly practised, chiefly in Finland, Norway and Sweden. Danish colleagues have more and more begun to use radiotherapy in early stages and a comparative study of primary expectancy vs. radiotherapy has been begun.

3.7 SPCG-4

The necessity of comparing radical prostatectomy with primary expectant management is evident from the above remarks. For ethical reasons, patients who have undergone surgical lymph-node exploration should not be randomised to non-interventional observation. Randomisation therefore must be made without knowledge of lymphatic dissemination and nodal evacuation confined to patients assigned to prostatectomy. The patients who should be considered are those with well or intermediately differentiated (T0d-T2) prostate cancer, the only exception being strictly localised (T01) tumour discovered at operation for lesions diagnosed as benign prostatic hyperplasia. Each collaborating centre decides if only patients aged ≤ 70 years shall be recruited, or if otherwise healthy men aged 70-74 years can also be included.

4. AIMS

4.1 Primary

The chief purpose of the study is to clarify if mortality from prostatic cancer is lower after radical prostatectomy than with primary expectant management. The main measure of effect consequently is survival rates, corrected for deaths from causes other than prostatic cancer.

4.2 Secondary

4.2.1 Metastasis-free survival.

4.2.2 Progression-free survival after treatment of progression.

4.2.3 Local tumour progression

4.2.4 Transrectal ultrasound and histology/cytology to be evaluated in a special spin-off project (appendix 1).

4.2.5 Quality of life and health service requirements evaluated in a special spin-off project (appendix 2 A-B).

5. PATIENT SELECTION

5.1 General aspects

Urologists who agree to collaborate in the study shall aim to include all patients who fulfil the requirements for randomisation. No randomisation shall be made until all inclusion criteria are satisfied. This means that definitive reports from cytological or histological examination have been received and the search for metastases is concluded.

5.2 Number of patients 700

The total of randomised patients shall reach 520 before recruitment ceases. Each centre shall randomise so many patients that it is reasonable to assume that all consecutively eligible cases were considered for inclusion in the study.

5.3 Enrolment criteria

The prostatic tumour shall be primary **adenocarcinoma**. The tumour shall be newly diagnosed, morphologically (by cytology and/or histology) confirmed, and untreated. It is highly desirable that both fine-needle (0.9 mm) biopsy (can be done without transrectal ultrasound) and core biopsy are taken from the actual tumour and from areas with "normal" tissue. DNA analysis should be performed, possibly via referral to appropriate laboratory or by later analysis of frozen or fixed tissue specimen. No more than four months shall elapse between definitive diagnosis and randomisation.

5.3.2 Re handling of **biopsy and serum specimens** see appendix 1.

5.3.3 The patient's **age** at the time of randomisation shall be less than 75 years. Each collaborating centre shall decide if recruitment shall be limited to patients aged up to 70 years or shall include otherwise healthy patients aged up to 74 years.

5.3.4 The patient's **general condition** and mental status shall permit observation in accordance with the follow-up protocol.

5.3.5 The patient shall not have **other** (malignant or benign) **disease** that could definitely (ASA I-III²³) increase the surgical risk or appreciably shorten life expectancy compared with men of corresponding age in the background population.

5.3.6 Local tumour stage **T0d, T1 and T2** (UICC 1978). T0i implies < 5% tumour tissue in the specimen, and T0d > 5%. The basis for T-classification is TUR-P biopsy (T0) or palpation. In TUR-P cases, six "blocks" of prostatic tissue should be studied. If transrectal ultrasound is available, it is used to supplement the T-classification.

5.3.7 The tumour shall be of high or intermediate **differentiation grade**. Therefore patients with poorly differentiated tumour cannot be included. *With an extended biopsy protocol (> 6 biopsies), patients can be accepted if < 25% is Gleason IV and < 5% Gleason V.*

5.3.8 With all results from the following investigation available, the patient shall be judged free from metastases, i.e. **stage M0**:

- Chest radiographs - no metastases. (*optional*)
- Bone scan - supplemented if necessary with radiographs of scintigraphically suspected lesions - no metastases.
- No sign of stasis in the upper urinary tract at scintiscan and/or urography.
- PAP < 150% of upper normal limit or acid phosphatase within normal limits. PSA values < 50 accepted.

6. STUDY PLAN - RANDOMISATION

- 6.1 Patients meeting all enrolment criteria are randomised with equal distribution to two parallel groups. Randomisation is done in blocks for each centre, with the number of patients in each block unknown to the investigators.
- 6.2 Stratification is made for high and intermediate cancer differentiation.
- 6.3 Randomisation is made at the study's secretariat in Uppsala or, for Finland and Norway, from the agreed national centre (communicated by telephone).

7. TREATMENT

7.1 General aspects

The practical management of patients who preliminarily satisfy the inclusion criteria is decided by the local organisation. A well thought-out strategy, however, is decisively important for maximal recruitment and for representative and optimal composition of the study.

7.2 Treatment options

7.2.1 Expectantly managed group

No immediate treatment (apart from TUR-P).

Patients receive information as in item 16. If the suggested management is not accepted, the patient is treated as in the "operation group". Follow-up charts kept.

7.2.2 Operation group

Surgery consists of pelvic lymph-node evacuation according to Paulsson et al.¹⁶ with Walsh-Lepor radical prostatectomy¹¹ if no nodal metastases are found. Radicality is more important than preserved potency. This often leads to inclusion of neurovascular bundle in the tumour side of the specimen.

Information as in item 16. If the patient agrees to undergo exploration and possibly radical operation (i.e. gives informed consent), the operation shall be performed within two months after randomisation. If the patient does not accept the suggested treatment, he is assigned to expectant management.

Follow-up charts kept.

7.2.3 Handling of surgical specimens

- 1 The prostatectomy specimen is provided with a perforated plastic tubing stump in the urethra.
- 2 A 4 x 20 mm punch biopsy is made in the palpable tumour (Biopty). This specimen is frozen in isopentane carbon dioxide ice and stored at -90°C until analysed (DNA, as yet undecided markers).
- 3 The specimen is mounted in a special jig (ad modum Mikael Häggman),
- 4 fixed for at least three days in 10% buffered formalin (pH 7.2),
- 5 then removed from the formalin, dried with cellulose and stained carefully and abundantly with Indian ink.
- 6 The specimen is cut into 5 mm thick slices numbered 1 - from the distal end. The first and the last slice are cut as right, left and middle, so that the resection surfaces are visualised (see Fig. 1 in appendix 1).
- 7 The slices are coarse-cut.
- 8 Tumour grade (WHO + Gleason score) and extent are noted for each slice, which is reviewed in four quadrants, each with an outer and an inner zone (fig. 2 in appendix 1).
- 9 Growth into or through the "capsule" is noted, also perineural (only extracapsular) growth, and invasion of fat or lymph glands. Length of any tumour growth along blood vessels recorded (mm).
- 10 Growth out to the resection surface (to the black stain) is noted and constitutes the criterion for non-radical extirpation.

7.3 **Adjuvant therapy**

The possible effect of adjuvant local (irradiation, laser) or systemic treatment (chemotherapy, additive hormonal, medical or surgical ablative) in early prostatic cancer is not known. As such treatment thus can preclude reliable evaluation, it will not be used within the framework of this controlled study.

7.4 **Treatment of locally recurrent or progressive tumour growth**

7.4.1 This concerns only management of patients without distant metastases. In the expectantly managed group, local progression denotes transcapsular tumour growth. After radical prostatectomy local recurrence is registered when morphological study of a suspected palpatory finding shows cancer growth.

7.4.2 For symptom-producing local tumour growth, TUR-P is standard procedure in the expectant management group. In symptom-producing recurrence and/or uraemia, orchidectomy is considered. Because of the incontinence risk, caution should be exercised with TUR-P in the radically operated group. For the rare cases of symptomatic local progression orchidectomy is contemplated.

7.5 **Treatment of distant metastases**

7.5.1 If treatment is indicated because of concomitant disseminated and local tumour growth, local treatment shall, if possible, await the effect of systemic treatment.

7.5.2 The principles for treating disseminated disease shall be the same in all participating centres for the two groups (expectant management and operation). Orchidectomy is primarily recommended. Differences in treatment principles between centres can be accepted, but high-dose oral oestrogen treatment should be avoided because of its well-documented side effects.

8. **FOLLOW-UP**

8.1 The patients shall be observed for at least ten years after randomisation (evaluation is made after five years). The special follow-up forms shall, if possible, be kept by the urologists engaged in the study.

8.2 All randomised patients shall be followed up according to the protocol, whether or not they complete the scheduled treatment.

8.3 The intervals for routine follow-up with report to the secretariat shall be six months in the first two years and one year in the remainder of the observation time. The follow-up form is completed each time and sent to the secretariat within two weeks. Clinically indicated re-examination can of course take place at shorter intervals, but need not be reported to the secretariat if the findings do not concern primary or secondary purposes of the study.

8.4 The extent of each follow-up examination is recorded on the special form. In summary, follow-up comprises:

8.4.1 **Postoperative course**, recorded on the operation report. This is not sent to the secretariat until a month after the operation, when the PSP is known and the course in the first postoperative month can be surveyed.

8.4.2 **Clinical examination**, with findings recorded on each occasion.

8.4.3 **Bone scan, chest radiography** and possibly **ultrasonography** of the prostate, performed one year after randomisation and then annually.

8.4.4 **Blood sampling** for determination of haemoglobin, serum creatinine, acid phosphatase (PSA, PAP or enzymatic) and alkaline phosphatase, six months and one year after randomisation and then annually.

8.4.5 **Extended search for metastasis** undertaken when indicated by other findings

9. DEFINITION OF CLINICAL EVENTS

9.1 Cause of death

Autopsy, if possible with serial sectioning and histological examination of the prostate and pelvic lymph nodes, should be requested. Pathology departments should be asked to note specially if a case coming to autopsy is included in the study.

The following classification should be attempted:

- Dead from prostatic cancer.
- Dead with locally recurrent or metastatic prostatic cancer, but other main cause of death.
- Dead without evidence of tumour recurrence.
- Postoperative death in hospital or within a month after operation.

Evaluation of corrected survival time to be made both with and without regard to postoperative death.

If unambiguous use of this classification is difficult, the case is judged by the project group, who decide the cause of death without knowledge of the patient's grouping in the study.

9.2 Distant metastases

At assessment after each follow-up examination the patient is categorised as having

- no distant metastasis
- suspected distant metastasis, or
- confirmed distant metastasis.

9.3 Local tumour progression

At each follow-up the patient is also categorised as follows:

9.3.1 In the expectant management group:

- No local tumour progression.
- Local progression with palpable transcapsular tumour growth and/or symptom-producing obstruction to flow necessitating TUR-P or catheter treatment.

9.3.2 In the surgical group:

- No local tumour progression.
- Local progression with morphologically confirmed tumour growth.

9.4 Quality of life (appendix 2A)

10. TIME PLAN

10.1 The study commences in 1989 and will be open for participation until the number of centres is considered adequate. The aim is that the number of participants will permit completion of enrolment during a four-year period.

10.2 Interim evaluation will be made when 300 patients have been enrolled. If this shows significant difference ($p < 0.02$; log rank test) in survival between the surgically treated and the expectantly managed group, the question of early conclusion of the study will be discussed. The choice of significance level presupposes two planned interim evaluations, the other made one year after termination of enrolment.

10.3 Complete analysis of the cases to be made five and ten years after termination of enrolment.

11. ETHICS

11.1 At each participating centre the treatment programme shall have been approved by the local or regional ethics committee. For this consideration it should be emphasised that the information to patients follows the model described by Zelen²⁴, implying that only the surgically treated group receive full information. ***All patients are informed of the three possible treatment strategies (expectancy-radiation- surgery).***

11.2 Informed consent shall be given by all the patients randomised to the surgical group.

11.3 The design and performance of the study accord with the Helsinki declaration of 1964.

12. STATISTICS

12.1 Size of study material

The cumulative corrected survival in the experimental group after five-year observation is assumed to be 85%. We wish to confirm a reduction of mortality from prostatic cancer in the surgical group leading to a corrected five-year survival of $\geq 95\%$. The risk of type 1 error is accepted as 5% with two-sided test. The risk of type 2 error shall be 20%, corresponding to a power of 80%. In these circumstances, 233 patients are required for each group, i.e. a total of 466 analysable cases. This number is calculated on the assumption that 90% of the patients accept the management proposal to which they have been randomised. Dropout due to faulty randomisation is expected to be at most 10%. To make good that dropout, 520 patients will be included in the study. ***With 700 patients, a difference of 5% can be identified after 10 years of follow-up.***

12.2 Interim evaluation

Interim assessment as a basis for possible early termination of the study shall be made as described in item 10 (Time plan). Another interim evaluation will be made after all 520 patients have been randomised and observed for at least one year. Analysis will be made ***after the last enrolled patient (no. 700) is included and thereafter every third year.***

12.3 Statistics

Because of its design, this study is primarily of "management" type, thus following the principle of "intention to treat" and with evaluation based on all randomised patients. For the analysis, patients are included in the group to which they were randomised, regardless of whether or not they accepted the proposed form of treatment.

12.4 Analysis

The statistical analysis will be made with unidentified treatment groups and led by Professor Reinhold Bergström.

13. ADMINISTRATION

13.1 Secretariat

The study's secretariat will be located at the Department of Urology, University Hospital, Uppsala, tel. 18/66 45 43. (Research secretary Eva Ahlstav). All randomisation and registration of patients from Swedish centres will be made there. Randomisation of patients from Finland or Norway can be done also at respective national centres. ***(From 1.8.1997 all randomisation is done at the Karolinska Institute, tel. 08/728 6892).***

13.2 **Project group**

The study is conducted by a project group responsible for decisions in all fundamental questions. The group includes a urologist from each participating centre. Meetings of the group are convened when required, but at least once yearly.

13.3 **Leadership group**

The group consists of Jan-Erik Johansson, Hans-Olov Adami, Lars Holmberg, Fred Helgesen and Bo Johan Norlén. It deals with questions arising in the study and is responsible for supervising data quality and the secretariat. The leadership group shall take initiatives for the scientific evaluations stipulated in the protocol.

Reference pathologists: Christer Busch, Uppsala, Hans Nordgren, Västerås and Björn Risberg, Örebro.

13.4 **Reference group**

The reference group includes, in addition to the members of the project group, all staff at each participating centre who contribute to the study more than required by their routine duties. Inclusion in the reference group requires involvement in both care and follow-up of randomised patients and in the study's scientific issues. It is the responsibility of the project group to ensure that the secretariat has an up-to-date list of representatives in the reference group.

14. **REPORTING**

- 14.1 All publications based on the clinical material are issued by SPCG and all participating centres and presented in the name of the project group. An addendum to each publication cites the reference group, clearly stating which members have actively contributed to processing the study and presentation of the manuscript. The project group can decide that author(s) may be named, if this is important for academic reasons.
- 14.2 Co-authorship of publications analysing special aspects, e.g. quality of life, utilisation of health services and prognostic factors, shall be discussed between those collaborating in the project. The guidelines of the Swedish Medical Association²⁵ essentially apply.
- 14.3 Each centre may use the study material for regional or local information in lecture form, but always stating which clinics have participated.
- 14.4 The result of the first interim evaluation shall be published only if the analysis leads to discontinuation of the study. Otherwise the result is made available only to the leadership group.

- 14.5 Locally initiated component projects within the study can be published by the respective member(s) of the project group.

15. FINANCE

- 15.1 Grants from the Swedish Cancer Society will cover the main costs of the study, including central administration, protocol printing, secretariat, data processing, etc.
- 15.2 Individual centres are responsible for their costs for any special resources or extra expenses. The same applies to costs for others than the project group`s members for travel to meetings associated with the study.

16. INFORMATION TO PATIENTS

16.1 Background

The study is based on the hypothesis that mortality from prostatic cancer is lower after radical prostatectomy than with primary expectant management. The hypothesis applies in specific circumstances, viz. locally limited and well or intermediately differentiated cancer without evidence of local lymph-node or distant metastasis. Further, it is assumed that the merits of radical treatment adequately compensate possible demerits, e.g. arising from postoperative morbidity.

The profound difference between the two therapeutic options to be compared - primary expectant management versus radical prostatectomy - entails considerable problems of information. We believe that an exhaustive discussion would often conflict with the view in the Helsinki declaration that information should not be given if it could be deleterious to the patient. To circumvent the problems, we used the method proposed by Zelen²⁴ for randomising and informing patients. Thus, instead of obtaining informed consent from all patients satisfying the inclusion criteria (Fig. 1), only those randomised to the experimental treatment (prostatectomy) are given complete information (Fig. 2). Patients who then refuse surgery are offered primary expectant management, i.e. standard treatment. (In the scientific analysis, however, such patients are included in the group to which they were randomised). The ethical motives for this study design were discussed in detail by Zelen²⁴ and others.

- 16.2 At most of the centres which considered participation in the study, expectant management currently is standard procedure, and consequently radical prostatectomy is the experimental treatment whose effect the study was designed to clarify. The following suggested information to patients was composed from that perspective. During the preliminary work, however, it emerged that at some centres radical surgery has been established as standard treatment. At these clinics there is no formal obstacle to classifying expectant monitoring as the experimental treatment; the study design is not thereby affected. The information given to patients, however, should be modified so

that those randomised to the watchful waiting group receive a fuller account of the treatment options.

16.3 **Information to the expectant management group**

Your tumour is in an early stage and the outlook is good. Various treatment methods have been tried for tumours of such stage, but none with conclusively established effect. We therefore suggest that you undergo regular and careful observation by a small group of doctors who are specially interested in prostate cancer and will suggest treatment if it becomes necessary. So that we can learn more about prostatic cancer, the results of this observation will be studied together with those from a number of centres in the Nordic countries.

16.4 **Information in the surgical group**

Your tumour is in an early stage and the outlook is good. A number of treatments have been tried for these early-stage tumours, but they have not yet been finally evaluated. If treatment is to be given in your case, we believe the most promising method to be removal of the whole prostate gland, which we hope can prevent the tumour both from growing locally and from spreading to other parts of the body.

This operation is done in two stages. In the first stage we search for any spread of the tumour to the lymph glands near the prostate. If no such spread is found, the operation is continued by removing the whole prostate gland. The operation is a fairly major one, but we judge your general health to be good enough for it to be done with little risk.

In a few cases the operation gives rise to difficulty in bladder control. With modern technique, however, this risk is small. There is also a relatively high risk that your sexual potency will be reduced by the operation.

We suggest that your tumour should be treated with this operation. But you have every right to refuse the operation, and in such case we shall only keep the tumour under observation

As it is important to learn more about prostate cancer, the results of continued observation in your case will be included in a large study from a number of centres in the Nordic countries.

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SPCG-4**REGISTRATION p. 2 (2)**

Code no. _____

2. GENERAL

Height, cm _____ Weight, kg _____

Preoperatively potent ___ yes ___ no

3. TUMOUR DETECTION

- screening
- incidental finding at routine examination
- unexpected finding at TUR-P
- examination because of symptoms
 - disturbed micturition
 - other _____

4. RANDOMISATION

Patient randomised (date) year month day to:

- Expectant management group
- Prostatectomy group

Patient's reception of information

- Accepted after standard presentation
- Accepted after more extensive presentation
- Declined surgery; referred to primary expectant management.

5. NON-RANDOMISED PATIENTS (CONCERNS ONLY PATIENTS SATISFYING THE INCLUSION CRITERIA BUT NOT INCLUDED IN THE STUDY)

- Before randomisation the patient expressed a wish/demanded not to be treated.
- Before randomisation the patient expressed a wish/demand for surgery.
- The patient was not considered for inclusion in the study, for the following reasons. _____

Signature

SPCG-4**OPERATION REPORT p. 2 (2)**

Code no.

3. PATHOLOGIST'S REPORT

Date year month day Report no. _____

Hospital: _____

Tumour size, mm _____ x _____ x _____

stage ___ T01 ___ T0d ___ T1 ___ T2 ___ T3 ___ T4

differentiation _____

Infiltration of seminal vesicles _ yes _ no

Transcapsular growth _ yes _ no

Radical excision _ yes _ doubtful _ no

Other findings: _____

SPCG-4**FOLLOW-UP**

Date: year month day

Code no. -----

Patient`s identity data (stamp)

To be sent to Eva Ahlstav, Cancer Epidemiology Unit, University Hospital, 781
85 Uppsala**Clinical condition**

- asymptomatic
- symptoms

Tumour status

- T0
- T1 Local progression (25% increase)
- T2
- T3 s
- T4

Scintiscan

(annual)

- normal
- metastasis progression regression
- suspected metastasis --- for observation. Radiography

 no scintiscan**Chest radiography**

(annual)

- normal
- metastasis

Treatment

- TUR-P
- orchidectomy
- other _____
- no treatment

Laboratory tests(at 0, 6, 12, 18, 24
36, 48 months, etc.)

- haemoglobin
- creatinine
- alkaline phosphatase
- PSA _____, or PAP _____, or acid enzyme _____

Summary

- No metastasis Suspected metastasis
- Definite metastasis Local progression
- other

Complication(s) associated with prostatic cancer