

APER

Abdomino Perineal Extralevator Resection

A registry based study of clinical results and of health and wellbeing in patients after abdomino-perineal resection for rectal cancer

Version 3. 2010-06-14

CONTENTS

1. STUDY ORGINASATION

1.1 Planning group:

Eva Haglind, MD, PhD, Professor, Department of Surgery, Sahlgrenska University Hospital/Östra and Sahlgrenska Academy

Eva Angenete, MD, Department of Surgery, Sahlgrenska University Hospital/Östra and Sahlgrenska Academy

Martin Gellerstedt, PhD, Statistician

Anneli Ambring, PhD, Health economist

Mattias Prytz, MD, NU-sjukvården/Norra Älvsborgs Hospital and Sahlgrenska Academy

Dan Asplund, MD, Department of Surgery, Sahlgrenska University Hospital/Östra and Sahlgrenska Academy

Jacob Rosenberg, Professor, Departemtn of Surgery, Herlev Hospital/Copenhagen University

Jane Heath, RN, Research nurse, Department of Surgery, Sahlgrenska University Hospital/Östra and Sahlgrenska Academy

Elisabeth Gonzales, RN, Research nurse, Department of Surgery, Sahlgrenska University Hospital/Östra and Sahlgrenska Academy

Ingrid Höglund-Karlsson, RN, Research nurse, Department of Surgery, Sahlgrenska University Hospital/Östra and Sahlgrenska Academy

Stefan Skullman, MD, Associate professor, Skaraborgs Hospital/Skövde

Zoltan Läckberg, MD, NU-Hospital/ Trollhättan

Peter Matthiessen, Associate professor, Örebro University Hospital, Örebro

1.2 Principal investigator: Eva Haglind

1.3 Deputy principal investigator:

1.4 Study secretariat

SSORG/Göteborg at Department of Surgery, Sahlgrenska University Hospital/Östra, Göteborg.

1.5 Steering committee

A planning group consisting of research nurses Jane Heath, Elisabeth Gonzales and Ingrid Höglund-Karlsson, principal investigator Eva Haglind, "post-doc" Eva

Angenete, MD&PhD and PhD student Mattias Prytz, MD as well as statistician Martin Gellerstedt, PhD and health economist Anneli Ambring, PhD. The study will report to SSORG at network meetings on a regular basis.

1.6 Scientific framework

The study is organised and performed within the framework of the Scandinavian Surgical Outcomes Research Group, a network of surgeons-scientists in hospitals in Sweden, Denmark and Norway. This network collaborates since 2008 in the formulation of scientific questions or hypotheses, writing protocols and in all parts of running trials. The first secretariat is situated in Göteborg. The website is www.ssorg.net

1.7 Writing committee

In agreement with internationally accepted guidelines for authorship the members in the planning group who are active in planning, running, analysing and writing will be part of the writing committee.

Publication of results is planned to be in an international "peer review" scientific journal.

2 PROTOCOL

1.8 Background

Rectal cancer is a common disease in the Western world. In Sweden 2000 patients are diagnosed each year. Together with colonic cancer ("colorectal cancer") it is the second most common cancer among both men and women. Rectal cancer has always had lower 5-year survival rates compared with colonic cancer, and although survival rates have improved over the last decade, there is still a difference. Further, rectal cancer probably comes with a higher risk of local recurrence, compared with colonic cancer. This type of recurrence, in the pelvis, is difficult to treat and often very painful and distressing for the patient. Patients with low rectal cancer (distal third of the rectum) undergo abdominoperineal resection (APR) ("amputation") with a permanent colostomy as an end result, and in most reports of results these patients have a worse prognosis and a higher risk of local recurrence than rectal cancer as a group.

For low rectal cancer patients the surgery will be combined with pre-operative radiation, short or long course and for a smaller group of patients long chemo-radiation preoperatively, for the so call ugly tumours. Some patients will undergo adjuvant chemotherapy after radical surgery, which for patients with metastais to local lymph nodes has been demonstrated to reduce the risk for recurrence.

In some trials of new therapeutic modalities health related quality of life has been studied, for example in the randomised trial COLOR II, where two different surgical procedures for primary, radical operation of rectal cancer are compared.

Other new surgical procedures have been suggested, also with the aim to improve outcome, one is the extralevator, cylindrical perineal excision as part of an APR. This operation could be regarded as the opposite of "minimally invasive"

compared to the established perineal operative procedure. One recent report claimed improved outcome in terms of circumferential margins meaning fewer cases with cancer growth in the circumferential margin, but the study design with historical controls with an unusually high frequency of engaged margins makes general conclusions impossible (West et al 2010). There is so far no evidence in support of the hypothesis of fewer local recurrences using the extralevator perineal excision. No trials seem to be underway regarding support for this interesting hypothesis. A Swedish multicentre trial was initiated in 2009, to test different ways to close the perineal wound after extralevator excision, but that study will not be able to demonstrate if the method as such is superior to traditional perineal surgical technique. Recently a health technology assessment (HTA) failed to analyse the method as there was no evidence published. However the HTA stated that studies are needed, and that this method should only be used if results of such surgery can be analysed.

There have been reports of case series regarding this method claiming high rates of wound infection and wound necrosis. There are also personal reports of walking problems, such as postoperative limping, for some variations of wound closing. In summary, there is a need for studies with the aim to evaluate the extralevator perineal excision method as part of an APR.

The quality registry for the treatment of colorectal cancer in Sweden allegedly includes all operated cases of rectal cancer. Into this registry details of preoperative staging, of treatment as well as details of the operation and postoperative adjuvant treatment are reported. Further details of the pathology report and the follow-up regarding reported recurrences at 3 years after surgery and 5-year survival can also be found.

In other studies we have used the Steineck concept to survey patient experiences of health and quality of life. We use specific questionnaires with detailed questions about experiences and symptoms, covering severity and duration as well as socioeconomic functioning. We have found that most patients are motivated to answer such questionnaires, with a compliance at 3 months >90% and at 12 months >85%.

1.9 The hypotheses:

Extralevator perineal excision in APR for rectal cancer will

- A. Decrease local recurrence at 3 years
- B. Increase postoperative morbidity
- C. Improve late morbidity
- D. Improve quality of life at 36-48 months postoperatively
- E. Increase resource consumption in comparison with the traditional perineal excision technique used in APR.

2.0 Primary endpoint.

2.0.1 Local recurrence rate at 3 years

2.1 Secondary end-points

- 2.1.1 postoperative morbidity: wound infection, deep infections, other infections, wound necrosis, pain, pneumonia, thrombosis.
- 2.1.2 re-operation/s, length of hospital stay/s, re-admittance/s and mortality, all within 12 months of primary surgery.
- 2.1.3 late morbidity and functional disorders: prolonged wound healing, late infections, limping, pain, sitting problems, urinary incontinence, erectile dysfunction, stoma related dysfunction
- 2.1.4 patient experienced health and QoL 24-48 months postoperatively
- 2.1.5 health economy analysis of resource consumption

2. 2 Organisation

This is a trial within the network SSORG and the primary intention is to identify a Swedish population from the colorectal cancer registry. The secretariat at Sahlgrenska University Hospital will send out requests for case history (index operation documentation) to all hospitals, and also contact all patients for send-out of questionnaires. The data base will be managed by the secretariat and application for permission to keep the database will be made to the appropriate hospital authority. An application will be made to the Ethical Committee in Göteborg. Each hospital with reported patients in the registry will be contacted in order to find documentation from case records about the type of perineal surgical method used at the index operation. The quality registry will be used for clinical data from the index operation and for local recurrence and survival data.

2.3 Study design

A registry based study of a three year cohort consisting of all patients who underwent APR in Sweden in 2007, 2008 and 2009. The quality registry for colorectal cancer will be used to retrieve information about the index operation, pathology report, recurrent disease and survival.

The two surgical procedures to be compared have been performed during the same time period, and a skewed population due to referral in order to get the “new” operation should be minimal during 2007 to 2009, as little was known about the technique. Some departments of surgery or even some surgeons had decided to use the new extralevator perineal excision for all their cases, whereas other departments/surgeons used the traditional technique.

To identify the surgical procedure and the more precise extent of extralevator excision during the index operation, a copy of the individual case record (surgery notes) for each patient will be collected from the operating hospital. To study the patient experience of health and well-being/quality of life a detailed questionnaire will be sent out, when 24-48 months after the index operation. The send-out will

be during the first half of 2011, resulting in varying times from index operation to answer.

2.4 Inclusion criteria

All patients registered in the colorectal cancer registry as operated by APR during 2007, 2008 and 2009 and who give informed consent.

2.5 Exclusion criteria

No informed consent received

2.6 Exclusion after inclusion

Only if a patient withdraws his/her consent after inclusion.

2.7 External validity

External validity is ascertained by identifying the population through the colorectal cancer registry. The small number of cases not reported in the registry will be missed, but as the reporting to the registry has already been done when the study opens, no surgeon bias should occur in relation to this particular study. Patients who are no longer alive at the time of entering the study population or at the time for send-out of the questionnaires will be identified through the National Population Register, in order to avoid misplaced contacts, which would be stressful for remaining family.

2.8 Patient information and informed consent

Before send out of the questionnaire, each patient still alive will receive a letter with information about the study and informing the patient that a co-worker in the study will shortly telephone the patient. In the telephone conversation the study worker will ascertain that the patient has understood the written information in the letter. After this the patient is asked if he/she consents and if the answer is yes the patient is further asked if we may send the questionnaire. If the answer is yes the questionnaire is sent. In the questionnaire contact addresses for the study are given and the patient is asked to call if she/he needs further information or has questions. Two weeks after send-out a thank you/remainder is sent, but after this no further active contact is made from the study personnel.

2.9 Pilot study

A retrospective study has been performed including all patients operated with APR at the Sahlgrenska University Hospital 2003 – 2009 (162 patients in all), where clinical data has been collected from case records and from the CRC registry. A follow-up will be made in 2010 by a questionnaire sent out to the surviving patients after approval from the Ethical Committee. At the Sahlgrenska University Hospital the extralevator perineal excision was introduced for all cases early in 2007 and the population consists of 81 traditional and 81 extralevator APRs. Preliminary findings are that wound infections, reoperations for wound complications and secondary wound healing were more frequently occurring after the extralevator perineal excision. The hospital stay was longer. The pathology

report included 18 lymph nodes (16 for traditional), but as the pathology technique was changed during this time period this finding is uncertain.

2.10 Participating hospitals

All hospitals with patients in the registry will be contacted in order to retrieve information about surgical procedure. All other clinical data will be collected from the database of the national CRC registries. No other input is expected by the hospitals.

2.11 Questionnaires

Patient self-estimate of health and well-being will be by using a specific questionnaire, developed in our group for this and later studies of rectal cancer treatment results. The basis for the questionnaire is the “Steineck concept” with questions about symptoms, their duration, intensity and severity. Questions about socioeconomic details are included and EQ5D as well, to facilitate health economy analysis. The questionnaire includes questions earlier used in other studies about health and wellbeing after treatment for gynaecological, urological and anal cancer, with additional new questions specific for rectal cancer and based on in-depth interviews with patients with rectal cancer treated by APR. The questionnaire will be face-validated and will also be used in a pilot study (2.10) of similar patients, before use in this study. The “Steineck concept” includes a special logistic, with a letter to the patient, followed by a telephone call to get consent from the patient before the questionnaire is sent out. Two weeks later the patient receives a “thank you” card which also serves as reminder for those who have not returned the questionnaire. We have found a compliance of approximately 90% using this process.

2.12 Work plan

Application to the Ethical Committees will be made in June 2010, and after approval data retrieval from the colorectal cancer registries is planned for the fall 2010. The questionnaire will be used in a pilot study at the same time. During the fall 2010 all hospitals will be contacted to ask for information about the operative procedure. During the first part of 2011 questionnaires will be sent out to all patients. Data on 3 year local recurrence should be in the quality registry by late 2013 and 5 year survival data will be available 2012-14.

2.13 Statistical Methods and power calculation

With inclusion of 900 patients, a difference of 5% in local recurrence can be shown if the lower level of recurrence is at 3-5% (80% power). If the lower level is at 7-10% a 7% difference can be shown with power 80%. This calculation is basically unchanged if the group sizes are 1:1, 2:1 or 1:2.

2.14 Data retrieval and registration

The secretariat will be at the Scandinavian Surgical Outcomes Research group unit in the Department of Surgery, Område 2, Sahlgrenska University Hospital, Göteborg

The database is based on full patient identity. The database is completely separated from the hospital patient record system and access is limited to the research personnel active in this study, using security measures such as user name and code.

Physically the database is placed as a document on a hospital server with username + code for entry. This ensures high security standards with automatic back-up of server data, fire walls against external violation etc. Application (xxx) to ”Personuppgiftsombudet” at Sahlgrenska University Hospital for the database.

2.15 Health economy

If there is found to be significant differences in clinical and QoL measures between the two surgical methods, a health economy analysis will be performed, using modelling, the results in the study and prices from the cost-per-patient system at Sahlgrenska University hospital as basis, in combination with sensitivity testing of results.

2.16 Ethical consideration

The study will be submitted for approval to the Ethical Committee (Etiska Prövnings Nämnden), in Göteborg.

The study will be registered in the study database <http://www.controlled-trials.com>, number xxxxxxxxxxxxxxxxxxxx.

Approval from the Swedish National Colorectal Cancer Registry has been applied for and informally given, however final application must include approval by the Ethical Committee.

2.17 Financing

The study is supported by grants from The Swedish Cancer Foundation (Eva Haglind) , ALF- grants at Sahlgrenska University Hospital (Eva Haglind). Application for ALF/HTA grant (VGR/Sahlgrenska Academy) has been submitted.

3 REFERENCES

1. S.O.S. Cancer Incidence in Sweden 2007. Statistics - Health and Diseases 2008:11, The National Board of Health and Welfare: 1-117.
2. Pahlman, L. et al. "The Swedish rectal cancer registry." Br J Surg 2007;94(10): 1285-1292.
3. MacFarlane, J. K. et al. "Mesorectal excision for rectal cancer." Lancet 1993; 341(8843): 457-460.
4. Kapiteijn E et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345(9):638-46.
5. den Dulk et al. "The abdominoperineal resection itself is associated with an adverse outcome: The European experience based on a pooled analysis of five European randomised clinical trials on rectal cancer." Eur J Cancer.2009;
6. Holm, T. et al. "Extended abdominoperineal resection with gluteus maximus flap reconstruction of the pelvic floor for rectal cancer." Br J Surg 2006; 94(2): 232-238.
7. West, N. P. et al. "Multicentre experience with extralevator abdominoperineal excision for low rectal cancer." Br J Surg 2010; 97(4): 588-599.
8. West, N. P. et al. "Evidence of the oncologic superiority of cylindrical abdominoperineal excision for low rectal cancer." J Clin Oncol 2008;26(21): 3517-3522.
9. Steineck G, Hunt H, Adolfsson J. A hierarchical step-model for causation of bias-evaluating cancer treatment with epidemiological methods. Acta Oncol 2006;45:421-429
10. Steineck G, Helgesen F, Adolfsson J, Dickman PW, Johansson JE, Norlén BJ, Holmberg L, Holmberg L; Scandinavian Prostatic Cancer Group Study Number 4. Quality of life after radical prostatectomy or watchful waiting. N Engl J Med 2002;347:790-796
11. Steineck G, Bergmark K, Henningsohn L, al-Abany M, Dickman PW, Helgason A. Symptom documentation in cancer survivors as a basis for therapy modifications. Acta Oncol 2002;41:244-252
12. Bergmark K, Henningsohn L, Steineck G, Avall-Lundqvist E, Dickman PW. Vaginal changes and sexuality in women with a history of cervical cancer. N Engl J Med 1999;340:1383-9.

4. ADDENDUM

1. CRF for retrieval of information from the Quality registry of colorectal cancer
2. CRF for retrieval of information from the case records of each operation
3. Questionnaire
4. Letter of information
5. PM for telephone call for consent and before send-out of questionnaire
6. Thank you and reminder letter