Abdominoperineal extralevator resection

A study of oncological outcome and well-being following abdominoperineal resection for rectal cancer – methodology

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ABSTRACT

INTRODUCTION: Abdominoperineal resection for distal rectal cancer is associated with a higher recurrence rate and a poorer overall prognosis than anterior resection. In order to improve the outcome, a more extensive procedure – extralevator abdominoperineal resection – has been introduced. There are, however, currently no prospective or registry-based studies on the effect of this new procedure on local recurrence rates.

MATERIAL AND METHODS: Abdominoperineal extralevator resection (APER) is a registry-based Swedish study investigating local recurrence rate three years postoperatively in the entire population of Swedish patients who underwent abdominoperineal resection or extralevator abdominoperineal resection in the 2007-2009-period. In addition to local recurrence rates, the study also investigates the functional and quality-of-life-related outcome 3-4 years postoperatively in the entire study population.

DISCUSSION: Distal rectal cancer is a surgical and oncological challenge. The APER study will be able to compare the two operative techniques (standard abdominoperineal resection or extralevator abdominoperineal resection) in terms of oncological and functional outcome.

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TRIAL REGISTRATION: The trial is registered at ClinicalTrials.gov, identifier NCT01296984.

PROTOCOL ARTICLE

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INTRODUCTION

Abdominoperineal resection (APR) is the surgical treatment in patients with distal rectal cancer in whom an anterior resection (AR) cannot be performed [1]. Studies show that the overall prognosis for these patients is inferior to that of patients undergoing AR, and that the local recurrence rates are higher [2, 3]. In order to address this problem, a more extensive surgical procedure has been proposed [4-6]. The procedure – described elsewhere and here referred to as the extralevator APR (eAPR) [4-6] – aims at creating a cylindrical specimen (**Figure 1**) without a "waist" in order to minimise the risk of involvement of the circumferential resection margin (CRM).

No randomised controlled studies compare the results of standard APR and extralevator eAPR. Previously published reports describe a decreased percentage of CRM involvement in eAPR compared with historical controls, but no studies demonstrate a decreased local recurrence rate with this new technique [5, 6]. Previous studies indicate an increased incidence of healing problems in the perineal wound following eAPR as compared with standard APR [6]. A retrospective study in our department shows no oncological short-term benefits from eAPR, but a significantly increased number of wound infections and also an increased number of reoperations due to wound complications [7].

The aim of the present study (APER) is to further investigate the key issue – i.e. local recurrence – and also to address the issues of self-estimated functional and quality of life (QoL)-related outcome on a national basis assessing the outcome in all Swedish patients operated with APR for rectal cancer in the 2007-2009 period. The primary endpoint in this study was the local recurrence rate after three years.

MATERIAL AND METHODS

Study objective and hypothesis

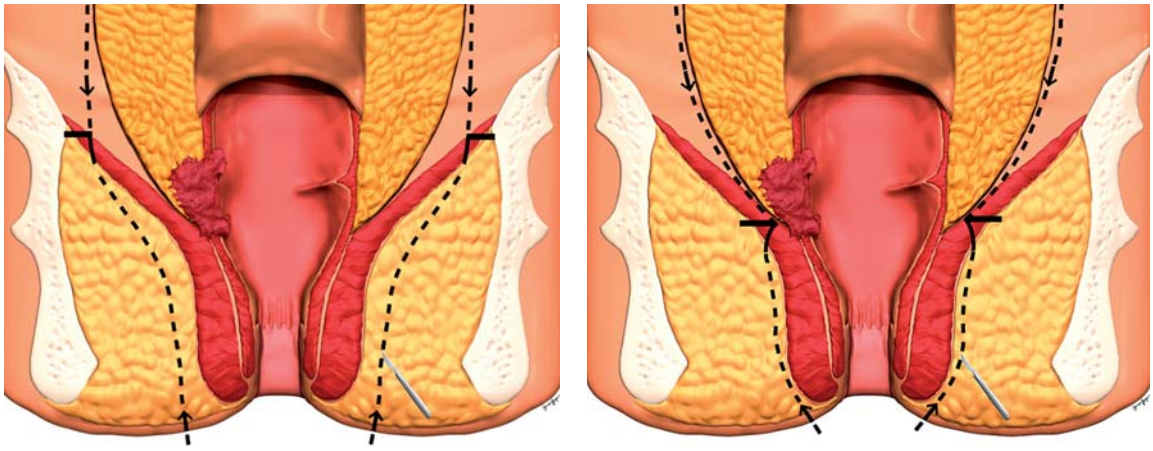
The primary objective of the present study is to evaluate if eAPR improves oncological outcome, measured as local recurrence, compared with standard APR. The secondary objectives are to evaluate the self-assessed functional and QoL outcome 3-4 years postoperatively, the postoperative morbidity and the resource consumption associated with the two surgical techniques.

The hypothesis is that eAPR decreases local recurrence at three years, increases postoperative morbidity, decreases late morbidity, improves quality of life at 36-48 months postoperatively and increases resource consumption in comparison with standard APR.

! ABBREVIATIONS

APR = abdominoperineal resection
AR = anterior resection
CRF = clinical record form
CRM = circumferential resection margin
eAPR = extralevator APR
QoL = quality of Life
pTNM = pathological Tumour-node-metastasis classification
TNM = tumour-node-metastasis classification

FIGURE 1



Extralevator abdominoperineal resection (left) and traditional abdominoperineal resection (right). Dotted lines indicate line of dissection. Horizontal lines mark where the abdominal dissection and the perineal dissection meet.

Endpoints

The primary endpoint is: Local recurrence rate at three years. The secondary endpoints are:

1. Postoperative morbidity within 30 days:
   a. Wound infection
   b. Deep infections
   c. Other infections
   d. Wound necrosis
   e. Pain
   f. Pneumonia
   g. Thrombosis
   h. Death
2. Within 12 months of surgery:
   a. Reoperation
   b. Length of hospital stay
   c. Re-admittance
   d. Mortality
3. Late morbidity and functional disorders:
   a. Prolonged wound healing
   b. Late infections
   c. Limping
   d. Pain
   e. Sitting problems
   f. Urinary incontinence
   g. Sexual dysfunction
   h. Stoma-related dysfunction.
4. Patient-experienced health and QoL 36-48 months postoperatively
5. Health economy analysis of resource consumption.

Inclusion and exclusion criteria

All patients registered in the Swedish Rectal Cancer Registry who underwent APR for rectal cancer (i.e. adenocarcinoma) in Sweden in 2007-2009 and who gave informed consent were included.

Patients who provided no informed consent were excluded. Furthermore, patients are excluded after inclusion only if the patient withdraws his/her consent after inclusion.

External validity

External validity was ascertained by identifying the population through the Swedish Rectal Cancer Registry. The registry has been validated [8, 9, 10] and has substantial coverage; approximately 98% of all Swedish patients with rectal cancer are reported [11]. A small number of cases not reported to the Registry will be missed, but as reporting to the Registry has already been concluded when the study opens, no surgeon bias should occur in relation to this particular study.

Data collection

From the Swedish Rectal Cancer Registry data will be collected on: preoperative tumour-node-metastasis (TNM)-classification, level of tumour from anal verge, patient demographics (weight, length and American Society of Anesthesiologists (ASA)-classification), pre- and post-operative non-surgical treatment, certain aspects of the operative technique (open or laparoscopic operation, level of vascular division), peroperative complications (including peroperative bleeding, perforation of the specimen), operating time, pathology report (including pathological tumour-node-metastasis (pTNM)-classification, CRM, distal margin, lymphnode harvest), postoperative complications (including infections, wound complications, cardiovascular complications, etc.), reoperations, postoperative intensive care treatment, re-admittance within 30 days and death within 30 days.

Postoperative wound infections and complications leading to post-operative intensive care treatment or

reoperations are reported to the registry. Prolonged wound healing is evaluated via the questionnaire, and time before complete wound healing and the period in which healthcare service are needed for wound treatment etc. are assessed.

Mortality at three years will be collected from the Swedish Civil Registry and checked against the medical files. Data on three-year local recurrence will also be drawn from the medical files as well as from the Swedish Rectal Cancer Registry.

The perineal dissection technique used is not reported to the registry. Operative notes on each patient are therefore retrieved from the hospital where the operation was performed. A Clinical Record Form (CRF) is used and points such as division of the levator muscle, removal of the coccyx – i.e. how the perineal part of the procedure was performed – are noted to determine if a standard APR or an extralevator APR was performed. It is also noted how the perineal repair was done. All retrieved operative notes are read and analyzed using the CRF. The operating notes are reviewed by one of the authors (MP). The operation is considered an extralevator APR if the operation was described in the operating chart as a "Holm procedure", if it was described as a cylindrical specimen or if it was stated that the levator muscle was dissected laterally or with a distance from the rectum. In cases where there was uncertainty as to how the dissection was done, operative notes will be reviewed by the other authors (EH and EA) separately. The operation type will be classified as "not stated" if no consensus is reached or if all agree that classification is impossible to determine.

We also register at what level the vascular division was made, if there was any damage to the specimen during the operation, if the perineal part was performed in lithotomy, prone Jack-Knife or other position and if the coccyx was resected.

Self-reported health-related quality of life

The patients' self-estimated health and well-being will be collected using a specific questionnaire developed in our group for this and other studies of rectal cancer treatment results. The basis for the questionnaire is the "Steineck concept" with questions on symptoms, their duration, intensity and severity [12, 13]. Questions about socioeconomic details are included as is the EQ-5D instrument to facilitate the health economy analysis. The questionnaire includes questions previously used in other studies about health and well-being after treatment for gynaecological, urological and anal cancer, to which are added new questions specific to rectal cancer based on in-depth interviews with rectal cancer patients treated with APR. The questionnaire has been face-validated and used in a pilot study on similar patients after which revisions were made before its use in the present study.

All patients will be checked in the Swedish Civil Registry before questionnaires are sent out to avoid misplaced contacts, for example with relatives of deceased patients, which could be distressful for the relatives. Each patient who remains alive will receive a letter with information about the study informing the patient that a member of the study staff will telephone the patient shortly. During the telephone conversation, the study staff will ascertain that the patient has understood the written information in the letter. Next, 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. The questionnaire will inform patients of the contact addresses of the study and patients are invited to call if she/he needs further information or if any questions arise. Two weeks after send-out, a thank you/reminder letter is sent, and after this there is no further active contact with the patient.

Health economy assessment

If significant differences in clinical and QoL measures between to the surgical methods are found, a health economy analysis will be performed using modelling. Clinical variables of interest comprise re-operation, re-admission and prolonged sick-leave. Prices from the cost-per-patient system at Sahlgrenska University Hospital will be used in combination with sensitivity testing of results.

Statistics

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 a power of 80%. This calculation is basically unchanged if the group sizes are 1:1, 2:1 or 1:2.

All data will be collected in a database and statistical analyses will be performed using SPSS 20.0 (SPSS Inc., Chicago, Illinois, U.S.A.). For comparison of the two surgical procedures regarding the incidence of local recurrence at three years, a bivariate analysis, i.e. χ^2-test, will be used. In order to adjust for potential confounding factors, a multiple logistic regression analysis will be done as well. Incidence of morbidity and functional disorder will be analyzed in the same manner. Established QoL-assessments like the EQ-5D will be analysed according to existing manuals and other QoL-data in a consistent manner. Adequate descriptive statistics, dependent on distributional shape and type of data, will also be produced. Generally, p values below 5% will be considered significant. The results will be presented

as mean values with minimum and maximum range in parenthesis.

Ethics

The study was approved by the Ethical Committee in Gothenburg, no. 406-2010.

Trial registration: The trial was registered at ClinicalTrials.gov, identifier: NCT01296984. Acronym: APER.

RESULTS

Data from the Swedish Rectal Cancer Registry have been retrieved for the 1,397 patients identified in the Registry. The send-out of the questionnaire was planned to take place in the fall 2011 and one and two years later for the patients operated in 2008 and 2009, respectively. Collection and analysis of operating notes is underway through contact with all hospitals in Sweden performing APR.

DISCUSSION

Local recurrence in rectal cancer is a disaster for the patient and the higher recurrence rate and inferior overall outcome for patients treated with APR – as compared with AR – have been and remain the focus of much of clinical rectal cancer research [14].

Holm et al [4] described the more extensive APR with a view to improving the oncological outcome in these patients. In these studies, the marker of oncological outcome was the pathology report on the surgical specimen with special focus on the CRM and the rate of involved CRM. Studies [5, 6] have shown that the extended APR in the hands of expert surgeons decreased the rate of CRM involvement and reduced the rate of intraoperative perforations compared with a historical material with a high rate of CRM involvement. In these studies , there seemed to be an increased rate of wound complications, and no analysis regarding functional outcome and QoL in the more extensive APR was reported [5, 6].

To thoroughly address the issue of local recurrence rates and to address the scientific question, group size is essential local recurrence rates should preferably be studied within the setting of a randomised trial. Representing a non-selected population, a national cohort can be regarded as the “second best” option. The Swedish Rectal Cancer Registry has a high coverage and by now a relatively long history and good validity [8, 9, 10]. This study has thus been set up to address the question of oncological outcome; it uses registry data and thereby achieves a high external validity. The registry does not include data on the perineal part of the operation; and in order to analyse the importance of this for outcome, operating notes are used and information is retrieved in a standardised manner by using a specific CRF. The registry also does not include data on QoL and details of functional outcome; and we will therefore employ a detailed and validated questionnaire sent to all patients in order to analyse the outcome of the two different procedures regarding these factors.

In summary, this study addresses – on a national basis – both the key issue of local recurrence rate and the issues of wound complications, functional and QoL outcome and health economy in the group of rectal cancer patients who undergoes APR, and we believe that it will bring useful information to help develop rectal cancer treatment for low rectal cancer.

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