1 Introduction
The main aim of this thesis was to investigate costs and effects of laparoscopy versus laparotomy in women with early stage endometrial cancer.

The first section in this chapter is an introduction on endometrial cancer, which is the most common gynaecologic malignancy. We discuss the surgical approaches by laparotomy and laparoscopy. Next, the history of minimal invasive surgery is outlined. Thirdly, the role of laparoscopic hysterectomy is discussed. Lastly, a brief overview of the content of this thesis is given.

**Endometrial cancer**

Endometrial cancer refers to several types of malignancies that arise from the endometrium, which is the lining of the uterine cavity. Endometrium consists of two types of tissue, epithelium and stroma. Endometrial cancer refers to cancer from the epithelial part of the endometrium. Endometrial cancer is the most common invasive neoplasm of the female genital tract and the fourth most frequently diagnosed cancer in women.\(^1\) Annually, 1400 new cases of endometrial cancer are diagnosed in the Netherlands and the incidence is increasing due to a rise in obesity and old age.\(^2,3\)

Endometrial cancer is a disease of the elderly and 90% of patients are over 50 years of age. The initial manifestation of endometrial carcinoma is postmenopausal bleeding and this is commonly an early presenting sign. Therefore most (75%-80%) endometrial carcinomas are diagnosed in the early stages. Because of this, prognosis of endometrial cancer is relatively good. The 5-year survival rate for endometrial cancer following appropriate treatment is 75% to 95% for stage I, 50% for stage II, 30% for stage III and less than 5% for stage IV.\(^4\)

The histopathology of endometrial cancers is highly diverse. The most common finding is a well-differentiated endometrioid adenocarcinoma, which is composed of numerous, small, crowded glands with varying degrees of nuclear atypia, mitotic activity, and stratification. This often appears on a background of endometrial hyperplasia. When detected in an early stage endometrioid adenocarcinoma is usually not disseminated. However, other subtypes of endometrial cancer exist such as the uterine papillary serous carcinoma and the clear cell carcinoma, which carry a less favourable course and prognosis.

Knowledge of the specific risk for each patient would allow better prognostication and potentially, individually tailored therapy. Extension of endometrial carcinoma to the cervix occurs in 10 to 15% of all cases of endometrial cancer. Since cervical invasion is recognized to increase the risk of pelvic lymph node metastasis, a more extended surgical procedure is recommended including lymph node dissection, performed by an gynaecological oncologists.\(^5-8\)

The cornerstone of the primary treatment for early stage endometrial cancer is surgery. Surgical treatment should consist of cytological sampling of the peritoneal fluid, abdominal exploration, palpation and biopsy of suspicious lymph nodes, abdominal hysterectomy, and removal of both ovaries and fallopian tubes. Pelvic and/or para aortic lymphadenectomy is not part of the standard treatment of early stage endometrial cancer in the Netherlands, according to Dutch guidelines and confirmed by recent studies.\(^9-11\)
Abdominal hysterectomy is recommended over vaginal hysterectomy because it affords the opportunity to obtain washings of the abdominal cavity and examine and palpate lymph nodes and abdominal structures to detect any further evidence of cancer. While removal of the uterus via the abdominal way is an accepted and effective treatment approach, morbidity of laparotomy can be substantial due to a high incidence of obesity and co-morbidity in this patient group. An alternative, less invasive approach for patients with early stage endometrial cancer might be laparoscopy.

History of minimal invasive surgery

The earliest record references to endoscopy date to ancient times with Hippocrates (460-375 BC). The first simple speculum for gynaecological endoscopy dates from the same time. Roman medicine also produced instruments with which they could inspect internal organs. Thus, the interest for physicians to look into the “internal organs” has existed since the early days of medicine.

The credits for modern endoscopy belong to Philipp Bozzini (1773-1809). He developed a light conductor which he called “Lichtleiter” to avoid the problems of inadequate illumination during endoscopy (Figure 1.1). In 1853, Antoine Jean Desormeaux, a French surgeon, first introduced the “Lichtleiter” of Bozzini into a patient. For many he is considered the “Father of Endoscopy.” This instrument had a system of mirrors and a lens, with a lamp flame as the light source; the endoscope burned a mixture of alcohol and turpentine. Burns, as might be imagined, were the major complication of these procedures. Several developments in the following years, which occurred independently but almost simultaneously, produced breakthroughs for endoscopy and laparoscopy that were the bases for modern instruments. In this period, incandescent light was invented. Maximilian Nietze (1848-1906) modified Edison’s light bulb invention and created the first electrical light bulb as the source of illumination in 1879 (Figure 1.1).

An important landmark in the history of laparoscopy was the year 1901. George Kelling, a surgeon from Dresden, coined the term “coelioscope” to describe the technique that used a cystoscope to examine the abdominal cavity of dogs.

During late 1910 and early 1911, H.C. Jacobaeus, from Stockholm, used the term “laparotheorakoskopie” for the first time. He also suggested employing similar techniques to examine body cavities endoscopically. Bertram M. Berheim, an assistant surgeon at Johns Hopkins, performed the first laparoscopy in the United States in 1911, before he learned of the work of Kelling and Jacobaeus.

Otto Goetze developed an automatic pneumoperitoneum needle characterized for its safe introduction to the peritoneal cavity for use in diagnostic radiology. In 1920, Zolillofer of Switzerland discovered the benefit of CO₂ gas to use for insufflation rather than filtered atmospheric air or nitrogen. Heinz Kalk, a German gastroenterologist, is considered the founder of the German School of Laparoscopy. In 1929, Kalk developed a 135-degree lens system and a dual trocar approach. He used laparoscopy as a method of diagnosis for liver and gallbladder disease.
In 1938, Janos Veress of Hungary developed the spring-loaded needle for draining ascites and evacuating fluid and air from the chest. Although, he did not suggest that it be used for laparoscopy. However, its current modifications make the “Veress” needle a perfect tool to achieve pneumoperitoneum during laparoscopic surgery. In 1944, Raoul Palmer of Paris performed gynaecological examinations using laparoscopy and placing the patients in the Trendelenburg position so gas could fill the pelvis. Harold Hopkins was responsible for the two most important inventions in endoscopy after World War II: the rod-lens system and fiberoptics.

During the 1960s, Kurt Semm, a German gynaecologist, invented the automatic insufflator. He played a major role in the development of laparoscopy. HM Hasson, a gynaecologist from the Grant Hospital of Chicago, developed a technique performing laparoscopy through a miniature laparotomy incision.

During the 1970s, gynaecologists had embraced laparoscopy, especially diagnostic laparoscopy and sterilization purposes (Table 1.1), and thoroughly incorporated the technique into their practice. General surgeons, despite their exposure to laparoscopy remained confined to traditional open surgery.

In England, in 1980, Patrick Steptoe started to perform laparoscopic procedures for oocyte retrieval in IVF procedures in the operating room under sterile conditions. In 1981, rules and requirements to perform laparoscopy were adopted by many hospitals and surgical societies. The American Board of Obstetrics and Gynecology made laparoscopy training a required component of residency training. In the Netherlands, Ad IJzerman, a gynaecologist from Eindhoven was the pioneer of the laparoscopic surgery, in close collaboration with colleague Kurt Semm.

The first solid state camera was introduced in 1982. This was the start of “video-laparoscopy (Figure 1.1).” Nothing had caused more revolution and had led to so many other developments during the past ten years than the first laparoscopic cholecystectomy in 1987. Phillipe Mouret performed the first video-laparoscopic cholecystectomy in Lyon, France. Since that year, laparoscopy wasn’t merely performed by gynaecologists, but also surgeons. Contributions of many surgeons have brought a new approach to surgery. However, once accepted as an alternative surgical technique for an indication, the laparoscopic technique was generally applied for other indications as well. Mostly, this occurred without proper evaluating feasibility and safety aspects of the laparoscopic approach for each specific indication.

Figure 1.1 development of laparoscopy

**Laparoscopic hysterectomy**

Nowadays, laparoscopy has developed into an important component of the operative gynaecological palette,
since it is accepted as an alternative to conventional open gynaecological surgery for many indications. However, the introduction of this new surgical technique has brought along difficulties incorporating this technique into daily practice. Although the diffusion of these procedures has increased over the last decade, the acceptance is still limited, especially for more advanced laparoscopic procedures (level 3). The level of difficulty of all endoscopic procedures has been divided into different strata by the Royal College of Obstetricians and Gynaecologists (Table 1.1).

In 1989, Harry Reich was the first to describe a laparoscopic hysterectomy and this complex surgical technique stimulated a general interest in the laparoscopic approach to hysterectomy. Despite previous small randomized and non-randomised studies demonstrating the feasibility and safety of laparoscopic hysterectomy for several reasons this approach is not an established procedure yet.\textsuperscript{15-24} The perception that laparoscopic procedures are more costly than open procedures has been a major reason for slow acceptance of laparoscopic surgery in general. Laparoscopy might be more costly due to longer operating time, expensive (disposable) surgical equipment and additional costs in case of conversion to laparotomy. Besides, only few gynaecologists have enough experience with advanced laparoscopic procedures e.g. total laparoscopic hysterectomy during residency and the learning curve is long. This complexity was illustrated by the results of a trial in women with benign disease, where the odds of having a major complication was twice as likely (OR 1.9; CI 1.11-3.28) for patients undergoing a laparoscopic hysterectomy versus laparotomy.\textsuperscript{25} To ensure a safe introduction of laparoscopic hysterectomy in established gynaecologists, a feasibility study was performed in the northern part of the Netherlands before starting a national prospective trial. It was investigated whether learning a laparoscopic hysterectomy by coaching and training on the job accompanied by an assessment was feasible and safe, reflected in the complication rate during and after the learning curve.

Taking into account safety and cost-effectiveness, RCTs represent the most important and informative trial design to help clinicians and their patients determining the optimum role for advanced laparoscopic procedures in current gynaecological practice. Therefore, a RCT was performed comparing laparoscopic hysterectomy versus the standard abdominal hysterectomy in early stage endometrial cancer patients in the Netherlands.

Outline of this thesis

Chapter two raises the question “how to safely introduce a new operative technique”? To answer this question, a well-designed randomized multicenter study is proposed in which total laparoscopic hysterectomy (TLH) performed by proven skilled surgeons is compared to total abdominal hysterectomy (TAH) in patients with early stage endometrial cancer. In this chapter we elaborately describe the study protocol of the randomized controlled surgical intervention study. The principles of developing and adhering to a protocol are approaches to improve the post-study probability and prevent the problem of publication bias. The relevance of this trial is stressed in two letters in response to studies published on surgical interventions in endometrial cancer.
Chapter three portrays the results of the multicenter randomized controlled trial regarding treatment-related morbidity and quality of life of patients with early stage endometrial cancer treated by laparoscopy or laparotomy. This study concerned a multicenter trial including 21 hospitals and 26 trained surgeons in the Netherlands. The primary outcome measure, major complication rate, was assessed by an independent complication review board. Quality of life was assessed by self-reported questionnaires administered before surgery and six weeks, three and six months after surgery.

In chapter four, a systematic review of twelve (randomized) controlled trials of a comparative evaluation of costs and effects of laparoscopic hysterectomy and abdominal hysterectomy for any indication of removal of the uterus is given. The type of cost analysis, perspective of cost analyses and all separate cost components of the studies were assessed. The direct and indirect costs as reported by the authors between the procedures and within studies were specified. To be able to draw a global conclusion with regard to costs and the ratio between costs and effects, overall treatment costs were estimated based on costs in the current situation in Dutch hospitals, with hospital stay and procedure related costs selected as main cost drivers.

In chapter five, a cost evaluation of two surgical approaches (TLH versus TAH), was carried out alongside our multicenter randomized controlled trial comparing TLH versus TAH in patients with early stage endometrial cancer. A proper economic evaluation from a broad societal perspective, including all relevant costs and effects should precede the process of implementing a new technique and be included in the decision process about the standard treatment.

Chapter six, subgroups of patients were constructed based on age, BMI, co-morbidity, previous laparotomy and FIGO stage and surgical technique (TLH or TAH) as predictors of major complications and conversion from laparoscopy to laparotomy, based on the data of 283 patients enrolled in the Dutch multicenter randomized controlled trial. For each subgroup of patients costs per major complication-free patient were estimated. In literature, it is often mentioned that patients with a high BMI and older patients benefit most from TLH. Aim of this study is to analyze whether data support this assumption.

Chapter seven discusses the role of endocervical diagnostic procedures in the preoperative staging of patients with adenocarcinoma of the endometrium. The main intent of accurate clinical staging is to establish a rational treatment for each individual patient. In our randomized controlled trial, only patients with early stage endometrial cancer (i.e., clinical stage I) were included. Before randomization, an endocervical curettage (ECC) has to be performed to exclude cervical involvement of endometrial cancer. To assess the accuracy of the endocervical curettage in preoperative staging, a retrospective study was performed on the histopathology results of preoperative endocervical curettage of 290 patients with clinical stage I epithelial endometrial cancer. We compared the results of the preoperative ECC with the final histopathology of the uterus.
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