Current and Future Status of Laparoscopy in Gynecologic Oncology

Derzeitiger und zukünftiger Stellenwert der Laparoskopie in der gynäkologischen Onkologie

Abstract

Laparoscopy is playing an increasingly important role in gynecologic oncology. The benefits of minimally invasive surgery for oncology patients and the quality of this treatment are well documented. Outcomes and quality of minimally invasive surgical procedures to treat cervical cancer were evaluated based on retrospective and case-control studies; outcomes and quality after minimally invasive treatment for early-stage low-risk endometrial cancer were also assessed in prospective randomized studies. If indicated, laparoscopic lymphadenectomy is both technically feasible and oncologically safe. Adipose patients in particular benefit from minimally invasive procedures, where feasible. The potential role of laparoscopy in neoadjuvant therapy for ovarian cancer and in surgery for early-stage ovarian carcinoma is still controversially discussed and is currently being assessed in further studies. Using a minimally invasive approach in gynecologic oncology procedures demands strict adherence to oncological principles and requires considerable surgical skill.

Introduction

The first use of laparoscopic methods in gynecologic oncology dates back to the 1970s. Initially, laparoscopy was used as diagnostic tool for preoperative staging in patients with ovarian carcinoma [1, 2]. In 1990 Querleu [3] first reported on the use of laparoscopy in pelvic lymphadenectomy procedures in patients with cervical cancer. Other reports soon followed, including a study on laparoscopy in paraaortic lymph node sampling, published by Herd an colleagues in 1992 [4], and a publication in the same year by Nezhad et al. [5] on laparoscopic radical hysterectomy to treat cervical carcinoma. Since then, numerous laparoscopic gynecologic oncology procedures have been carried out, and a number of studies have assessed the outcomes after minimally invasive surgical procedures. In the German Society for Gynecology and Obstetrics (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe [DGGG]), the Study Group for Gynecologic Endoscopy (Arbeitsgemeinschaft Gynäkologische Endoskopie [AGE]) promotes advanced training and scientific debate on the use of endoscopic surgery for all indications in surgical gynecology.

Zusammenfassung

To assess oncologic effectiveness, numerous studies have evaluated the number of resected lymph nodes and parametrial and vaginal resection margins in laparoscopic procedures compared to open surgery. The majority of these studies are retrospective analyses and their findings suggest that outcomes, as measured by these parameters, are equivalent [16–19].

An HTA report published in 2010 [20] and a systematic review published in 2012, which included data on 1339 laparoscopically operated patients from 21 studies [21], came to the same conclusion. Two prospective randomized studies differed from each other with regard to surgical technique and results. The study by Naik et al. [22] involved small stage IB tumors with 15 patients randomized to undergo laparoscopically-assisted radical vaginal hysterectomy (LARVH) or radical abdominal hysterectomy (RAH). The clinical short-term benefit of laparoscopically assisted procedures was confirmed, but laparoscopically assisted procedures were also found to be less radical, as the mean resected vaginal cuff (1.26 vs. 2.16 cm) and mean resected cardinal ligament (1.3 vs. 2.79 cm) lengths were shorter. Simsek et al. [23] carried out a prospective randomized evaluation of 88 patients, 35 of whom underwent laparoscopic total radical hysterectomy. Based on the parameters “number of resected lymph nodes” and “histologically verified, tumor-free vaginal and parametrial resection margins” in patients with parametrial involvement (11.4% of laparoscopic procedures and 16.9% of open surgical procedures), they found no difference in radicality compared to open surgery. The most important parameters from an oncologic standpoint are rate of recurrence and survival probability, and data on these parameters are plentiful, although all of the data come exclusively from retrospective and paired-cohort or case-control studies [24–29]. However, there are no significant differences between the findings in these studies and outcomes after open surgery (Table 1).

Prospective randomized survival data are not available in the literature making it impossible to do a Cochrane analysis offering definitive recommendations [30].

**Recommendations and guidelines**

The available data have found their way into national and international guidelines. The Scottish Intercollegiate Guidelines Network already stated in 2008 that laparoscopic vaginal radical hysterectomy was a safe and effective alternative to conventional abdominal radical hysterectomy to treat FIGO stage IB1 cervical cancer [31]. In its 2010 guideline, the National Institute for Health and Clinical Excellence in the UK presented sufficient evidence on the effectiveness and safety of laparoscopic radical hysterectomy to treat early-stage cervical cancer to support the use of this procedure [32]. The new German S3-Guideline on the Treatment of Cervical Cancer is, as yet, only available in its consultation-stage version; it states with a recommendation grade of 0 and a level of evidence of 2+ that laparoscopic radical hysterectomy can be an alternative procedure to abdominal open radical hysterectomy [33].
Endometrial Cancer

Current status of studies: laparoscopic vs. open surgery

Many articles have reported on the benefits of laparoscopic procedures rather than open surgery to treat early-stage endometrial cancer. Similar to cervical cancer, reported benefits generally include fewer perioperative complications, less loss of blood, fewer transfusions and shorter hospital times as well as a higher quality of life after laparoscopic hysterectomy compared to open abdominal hysterectomy; these findings were recently confirmed in a meta-analysis of 4 randomized controlled studies [34] and a Cochrane analysis of 8 prospective randomized studies with 3644 patients (Table 2) [35]. No statistically significant differences were found with regard to perioperative morbidity (RR: 0.76; 95% CI: 0.32–1.79), blood transfusion rates (RR: 0.55; 95% CI: 0.21–1.49), bladder lesions (RR: 0.49; 95% CI: 0.13–1.86), intestinal injuries (RR: 1.49; 95% CI: 0.39–5.72) and vascular injuries (RR: 0.43; 95% CI: 0.08–2.32). Blood loss was lower (RR: ~106.82; 95% CI: ~141.59 to ~72.06) and there were fewer serious postoperative complications (RR: 0.58; 95% CI: 0.37–0.91) in the laparoscopy group. From an oncologic standpoint, there were no differences between laparoscopic and open surgery with respect to disease-free interval (HR = 1.13; 95% CI: 0.90–1.42) and overall survival (HR = 1.14; 95% CI: 0.62–2.10). In the largest prospective randomized study carried out to date, the Gynecologic Oncology Group (GOG) LAP2 study [36, 37], 2616 patients were randomly allocated to receive either laparoscopy or laparotomy treatment. The 5-year survival rate was almost identical in both groups at 89.9%.

The use of laparoscopy and laparotomy to treat high-risk endometrial cancer are compared in a retrospective multicenter study [38] and a prospective randomized study in the above-mentioned GOG LAP2 study. The study by Fader et al. also included patients with grade G3 tumors. Two thirds of patients were operated on using robotic minimally invasive surgery and one third underwent laparoscopic surgery. There were no differences with regard to age, comorbidities, BMI, previous abdominal operations, tumor stage, adjuvant therapy and histology. A comparison of the different operative techniques found no difference in disease-free interval and overall survival. A subgroup analysis done in the GOG LAP2 study also found no significant differences with regard to recurrence-free survival, even in the high-risk cohort (unfavorable tumor stage, myometrial infiltration of 50% and more, lymphangitic carcinomatosa, unfavorable histology). However, it should be noted that this subgroup analysis of high-risk cancers had not been defined in advance as one of the study endpoints and consequently lacks sufficient statistical power.

Recommendations and guidelines

The AGO recommendations [39, 40] include two statements on the use of laparoscopy to treat endometrial cancer:

- Examination of short-term postoperative morbidity shows that laparoscopy is superior to open surgery. The long-term morbidity is the same.” And
- “For low-risk cases the oncologic results for laparoscopic and open surgery are comparable. The data on high-risk cases is still insufficient”.

International guidelines, e.g. from the UK and France, also support the use of laparoscopy to treat endometrial cancer [41, 42], but they emphasize the importance of special training and the fact that surgeons must have advanced laparoscopic skills.

Risk factor obesity

Endometrioid endometrial carcinoma is strongly associated with obesity and diabetes mellitus. This represents a risk factor for perioperative complications, resulting in longer operation times, higher blood loss and higher transfusion rates. Laparoscopy is more difficult in obese patients. Access to the peritoneal space, establishment of pneumoperitoneum, and access to pelvic organs and structures and the paraaortic region can be more difficult, and anesthesiologic complications can be an impediment to lymphadenectomy and even hysterectomy procedures. Nevertheless, despite these difficulties, the success rate for laparoscopy procedures performed in obese patients with early-stage endometrial
cancer was 89%. Although the operation times were longer, there were significantly fewer postoperative complications compared to open procedures, and the subsequent quality-of-life score was higher [43–46]. It would therefore appear that laparoscopy is particularly suitable to treat obese patients. This is an important consideration as obesity represents a significant risk factor for postoperative complications in patients with early-stage endometrial cancer but does not appear to constitute an oncologic prognostic factor [46].

Lymphadenectomy in Uterine Cancer

Laparoscopic lymphadenectomy is as safe as open laparotomy to treat lymphadenectomy [19, 43, 44]. Most studies found no significant difference in the number of lymph nodes resected by laparoscopy or laparotomy. Oncologically acceptable pelvic and paraaortic lymphadenectomy can also be carried out using a laparoscopic approach (Fig. 2). Although laparoscopic conversion rates of up to 5% have been reported in the literature (and up to 12% of cases in obese patients), these laparoscopic conversions were rarely precipitated by the lymphadenectomy.

The morbidity associated with lymphadenectomy can be reduced with the use of the sentinel lymph node concept. Robust data on the use of this concept in patients with cervical cancer has shown that the sentinel lymph node technique is reliable in patients with tumors measuring less than 2 cm and that the technique can be carried out laparoscopically with satisfactory results [12, 47]. A sensitivity of 93.5% and a negative predictive value of 99.1% have been reported using technetium and blue-dye labeling, meaning that the technique can be used in clinical practice. Optimal bilateral sentinel lymph node detection combined with ultrastaging using histological sections and immunohistochemistry can additionally reduce the false-negative rate [48].

Use of sentinel lymphadenectomy in endometrial cancer is also being trialed. However, the studies published to date investigated different areas of application (cervix, subendometrial, intra-mural) and used different agents (technetium, blue dye or both). In a recent meta-analysis (2071 patients, 35 studies with information on false-negative rates, 51 studies with information on detection rates), the pooled detection rate was 77.8% (95% CI: 73.5–81.5%) and the pooled sensitivity was 89% (95% CI: 83–93%) [49]. Studies again confirmed the benefits of pathologic ultrastaging [50]. The current debate focuses less on the question of which operative approach to use (laparoscopy or open surgery); rather, controversy centers on the oncologic validity of the sentinel lymph node concept in endometrial cancer, and the method is not currently considered as established [49, 51–54]. Thus, in cases where histology or staging has indicated a need for lymphadenectomy, complete pelvic and paraaortic lymphadenectomy is still considered indispensable, even if sentinel lymph node biopsy has been performed and the findings are negative.

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<th>Table 2</th>
<th>Cochrane analysis for endometrial cancer (Galaal et al. 2012).</th>
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<tr>
<td>Outcome or subgroup title</td>
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<td><strong>Comparison 1. Primary outcomes</strong></td>
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<td>1 Overall survival</td>
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<td>2 Recurrence-free survival</td>
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<td><strong>Comparison 2. Secondary outcomes</strong></td>
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<tr>
<td>1 Perioperative death</td>
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<td>1.1 Within 30 days</td>
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<td>1.2 Within 6 weeks</td>
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<td>2 Estimated blood loss (ml)</td>
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<tr>
<td>3 Blood transfusion required</td>
<td>7</td>
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<td>4 Bladder injury</td>
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<td>5 Urethral injury</td>
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<td>6 Bowel injury</td>
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<td>7 Vascular injury</td>
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<td>8 Severe postoperative adverse events</td>
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Results of a survey on the use of laparoscopy to treat uterine cancer in Germany

AGE and AGO carried out a joint survey in 2012 to determine the prevalence of endoscopy to treat uterine cancer in Germany. As expected, endoscopy is much more common in procedures to treat endometrial cancer (around 80% of cases) compared to cervical carcinoma where endoscopy is only used in around 50% of procedures. The survey found that 58% of patients with endometrial cancer underwent total laparoscopic hysterectomy with adnexectomy and 32% had laparoscopically assisted vaginal hysterectomy with bilateral adnexectomy. Hospitals were asked about the numbers of patients operated on in their clinic using endoscopy and many hospitals stated that the majority of procedures (>75%) for endometrial cancer were done laparoscopically (46 hospitals, corresponding to 36% of participating hospitals). However, only 14 hospitals (11%) reported that procedures for cervical cancer were done laparoscopically. Given the greater technical skills required for this operation compared to procedures for endometrial cancer, this result does not come as a surprise [55].

Ovarian Cancer

The issue of using laparoscopic surgery to treat (presumed benign) ovarian tumors was already discussed controversially in the 1990s and finally led to the guideline “Laparoscopic Surgery of Ovarian Tumors” jointly supported by the AGE and AGO. This guideline was first published in 1998 and has since been revised twice, the last time in 2008. It was the first guideline ever issued by the German Society for Gynecology and Obstetrics (DGGG). The latest version of this guideline [56] includes the statement: “patients with the incidental finding of ovarian cancer should not undergo further laparoscopic procedures (except to confirm the diagnosis); the definitive operation should be immediately or subsequently by laparotomy”. The S3-Guideline on Diagnostics, Therapy and Follow-up of Malignant Ovarian Tumors published in 2013 [57] states that laparoscopic staging must not be done except as part of a study, due to the lack of controlled randomized data comparing laparoscopic and open procedures.

The literature on the use of laparoscopy to treat early-stage ovarian cancer goes back to case reports published in the early 1990s. Harry Reich was the first person to report a total laparoscopic hysterectomy procedure, describing the case of a patient who had refused open surgery and underwent laparoscopically assisted surgery instead [58]. Only a few years later, the introduction of laparoscopic lymphadenectomy with paraaortic lymph node resection allowed the technique to be evaluated as a tool for the staging of ovarian and Fallopian tube cancer [59], although the initial goal of these studies was simply to demonstrate the technical feasibility of the procedure. Right from the start, there were oncologic concerns about the laparoscopic means of access, particularly with regard to the emergence of port-site metastases in the region of the trocar puncture site, the risk of higher rates of intraoperative tumor findings, the validity of endoscopic staging and the oncologic outcome. Even in 2013, a Cochrane analysis came to the conclusion that the existing evidence is insufficient for a scientific evaluation of the benefits and risks of laparoscopy compared to laparotomy to treat early-stage (FIGO stage I) ovarian cancer [60]. However, this statement is based on a lack of randomized controlled studies.

The data on clinical feasibility is currently only available from non-randomized studies. The literature ranges from reports on laparoscopic procedures of early-stage ovarian cancer to studies on debulking procedures and the use of laparoscopy to treat recurrence [61]. In their search for an oncologically safe and technically feasible approach, a number of study groups appear to have changed their opinion in favor of a minimally invasive approach. Thus, in 1994, Canis et al. [62] were of the opinion that, because outcomes after using a laparoscopic approach to treat suspicious tumors were unclear, patients should undergo laparotomy. 10 years later [63] he and his colleagues held the opinion that restaging of early-stage ovarian cancer is a good indication for laparoscopy.

A recent publication from the United Kingdom described the biggest prospective single institution case series to date [64]. The study evaluated 35 patients with early-stage ovarian cancer operated on using a laparoscopic approach. The overall complication rate was 14% (5/35) and the conversion rate was 6% (2/35); overall survival was 100% and disease-free survival was 94% after a mean follow-up of 18 months (range 3–59). The authors concluded that laparoscopic staging was technically safe, oncologically acceptable and that the minimally invasive nature of the procedure meant that patients benefitted from a laparoscopic approach compared to laparotomy. An Italian study group arrived at similar results in a retrospective analysis of the data of 19 patients [65]. After a mean follow-up of 30 months (range 10–74), overall survival was 100% and disease-free survival was 84%. The mean number of resected pelvic and paraaortic lymph nodes was 17 (range 7–27) and 14 (range 8–21), respectively. A meta-analysis published in 2013 which looked at the data of 11 observational studies [66] reported a recurrence rate of 9.9% (95% CI: 6.7–14.4%) for a comparable mean follow-up time.

Currently laparoscopic procedures (Fig. 3) can still only be compared with outcomes after laparotomy on the basis of case-control studies. Chi et al. [67] reported on 50 patients, 20 of whom were treated by laparoscopic surgery while 30 underwent open surgery. There were no significant differences with regard to the number of resected lymph nodes or omental specimen size. Operation times were longer with laparoscopy (321 vs. 276 minutes); blood loss and hospital times were lower after laparoscopy and there was no significant difference in the complication rates. The retrospective comparative study of Lee [68] comes to similar conclusions, noting that the complication rate after laparoscopic staging was significantly lower (7.7%) than that of the laparotomy group (23.0%). In another retrospective study, Koo et al. compared 24 patients treated laparoscopically with 53 patients who underwent open surgery. There were 2 recurrences in each group during the follow-up of 31 months, which corresponds to a recurrence rate of 8.3% in the laparoscopy group and 3.8% after laparotomy. The disease-free interval reported for the laparoscopy group (59 months) did not differ significantly from that of the laparotomy group at 66 months (p = 0.367) [69]. A recently published Italian case-control study [70] which evaluated 35 patients treated laparoscopically and 32 patients who underwent open surgery also looked at the issue of tumor cell spillage and subsequent upstaging. Spillage occurred in 6 cases in the laparoscopy group and in 4 patients in the open surgery group and did not differ statistically between groups (p = 0.59; OR: 0.7; 95% CI: 0.38–1.27). Laparoscopy was associated with a significantly lower postoperative complication rate of 3% compared to 28% (p = 0.005). Five-year disease-free survival and overall survival rates were not affected by the surgical technique (p = 0.12 and p = 0.26, respectively; log-rank test). There were no differences...
in overall survival (OR: 0.5; 95% CI: 0.21–1.21). The authors concluded that laparoscopy was comparable to open surgery in terms of oncologic control but was associated with a lower perioperative morbidity.

The study of Fagotti published in 2013 [71] focused on a different aspect. In their study, laparoscopy was used to determine the feasibility of surgery in individual patients. No complications were reported after laparoscopy (exploratory staging laparoscopy). 148 of the 300 investigated patients were considered suitable for surgery and underwent laparotomy; R0 resection was achieved in 62.1% and reduction of the tumor to less than 1 cm in 22.5%. A recent Cochrane analysis also evaluated the same issue and included a total of 7 studies in their analysis. Despite a number of caveats because of the limited numbers of patients and the different concepts used in the available studies, the authors concluded that laparoscopy was a promising approach [72].

**Conclusion**

In summary, we can state that laparoscopy has an increasingly important role to play in gynecologic oncology surgery. The benefits of minimally invasive surgical procedures are also manifest for oncologic indications. Chief among these benefits is reduced postoperative short-term morbidity. Laparoscopic radical hysterectomy is an established alternative to abdominal open radical hysterectomy for the surgical treatment of cervical cancer. Benefits of laparoscopy include less loss of blood, fewer transfusions and shorter hospital times. Operation times are usually longer. Oncologic radicality and recurrence and survival rates are comparable for both approaches; however, the relevant data is still predominantly based on retrospective studies. Comprehensive prospective randomized studies attest to both the perioperative benefits and the oncologic equivalence of laparoscopy in low-risk endometrial cancer. Based on these data, the use of laparoscopic surgery is advocated in national and international recommendations and guidelines for the treatment of early-stage endometrial cancer.

If indicated, laparoscopic surgery is an oncologically safe and technically feasible procedure for systematic lymphadenectomy and sentinel lymph node biopsy. Obese patients in particular benefit from a minimally invasive approach. But problems with the technical viability of laparoscopy are higher in this patient population. In contrast to uterine cancer, the question whether to use laparoscopy in ovarian cancer is still controversially discussed; the current recommendation is that laparoscopic surgery should only be used to treat ovarian cancer in clinical trials. Numerous reports in the literature from well-known oncologic centers point to the potential use of laparoscopy for staging, including neoadjuvant therapeutic approaches, and discuss the feasibility of using laparoscopy in the surgical treatment of early-stage cancers. However, experience is still limited, and meaningful prospective randomized studies which could provide reliable information on oncologic outcomes over and above the feasibility of the procedure are still lacking.

It remains to be seen to what extent robotic procedures, which were not the topic of the present overview, will transform the range of procedures used in gynecologic oncology surgery in future.

It must be emphasized how important it is that surgeons carrying out laparoscopic procedures have the necessary expert technical skills, training and experience, a point which all recommendations and guidelines are also agreed upon as the prerequisite for these procedures. If available, then endoscopic surgical procedures represent a successful way of offering the benefits of minimally invasive procedures to patients without having to make compromises in terms of oncologic safety.

**Conflict of Interest**

None.

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