CERVICAL CARCINOMA: CURRENT ROLE OF LAPAROSCOPY

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ABSTRACT

This review aims to analyse and describe the current role of laparoscopy in the treatment of cervical cancer. Laparoscopy has become an important tool in gynaecological oncology. Its general advantages in comparison with open surgery apply to oncological patients as much as they do to benign conditions. Data from retrospective and case-control studies have proven that treatment of early cervical carcinoma is successfully feasible by means of minimally invasive surgery with no compromise of oncological principles nor radicality. Thus, laparoscopy has entered guideline recommendations as an alternative to open procedures when operative therapy is indicated. Nevertheless, laparoscopic radical hysterectomy, as well as lymphadenectomy, remain demanding and require surgeons experienced in both operative oncology and endoscopy.

Keywords: Laparoscopy, gynaecological oncology, early cervical carcinoma, radical hysterectomy, laparoscopic lymphadenectomy.

INTRODUCTION

The incidence of invasive cervical carcinoma has decreased in Europe over the last three decades due to screening programmes, and will probably decrease further with human papilloma virus vaccination. It is currently the fourth most common malignancy in women, behind breast, endometrial, and ovarian cancer, and accounts for only approximately 2% of all malignancies in women. Most invasive cervical carcinomas are at a low clinical stage when diagnosed, i.e. 62% at Stage I and 25% at Stage II.[1] According to current guidelines, primary therapy of the so-called early cervical carcinoma (Stages IA to IIA1) consists of a surgical approach.[2,3] Stage-dependent radical hysterectomy is essentially performed as described in 1974 by Piver et al.[4] and following the historic principles of Schauta and Wertheim and their modifications by Meigs, Latzko, and Okabayashi.[5-7] A widely accepted classification of radical hysterectomy for cervical cancer (CVC) was introduced in 2008 by Querleu and Morrow,[8] which defined four different types of radicality (A-D) based on lateral extent of resection and with subtypes considering nerve preservation and paracervical lymphadenectomy. Lymph node dissection is described separately in this classification as one of four levels (1-4) according to arterial anatomy.

The introduction of laparoscopy into treatment concepts for early CVC aims to reduce the considerable invasiveness and morbidity of these extensive surgical procedures. Pilot reports date back to 1990 when Querleu et al.[9] described pelvic lymphadenectomy in cervical carcinoma, followed in 1992 by the publication of para-aortic lymphadenectomy by Herd et al.[10] and radical hysterectomy by Nezhat et al.[11] Since this pioneering work, the role of minimally invasive surgery in gynaecological oncology has evolved and been the subject of numerous clinical reports and studies.

The aim of this review is to give an overview on data defining the impact of laparoscopic procedures in the framework of surgical therapy concepts for early CVC.

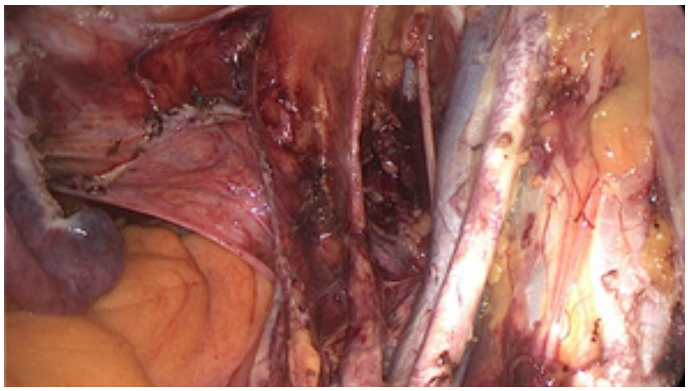

Figure 1: View of right pelvic fossa after laparoscopic lymphadenectomy.

ONCOLOGICAL CONCEPT OF THE SURGICAL APPROACH

Current guidelines recommend operative therapy according to the clinical stage of the disease.[2,3]

Simple hysterectomy is generally recommended in CVC of Stage IA1 without or with up to only one risk factor (G3, L1, V1). If fertility preservation is desired, (*in sano*) conisation with cervical curettage can be performed.[3,12] When risk factors are absent, the risk of lymph node involvement is very low and therefore lymphadenectomy is not indicated.

In Stage IA1 with at least two risk factors (G3, L1, V1), and in Stage IA2 with no more than one risk factor, pelvic lymphadenectomy is performed (Figure 1) because of an elevated risk of approximately 8% for lymph node metastasis.[13] The possibility of sentinel node biopsy may further reduce invasiveness in selected patients at this early stage of the disease, but does not represent a standard procedure. When lymph nodes are negative, extrafascial hysterectomy (Type A, Piver I) or, in the case of fertility preservation, conisation with cervical curettage follows without parametrial resection. In nodal-negative Stage IA2 with more than one risk factor, IB1 and IIA1 require radical hysterectomy with parametrial resection extending medially to the ureter by dissecting the uterine vessels at the ureteral crossing (Type B, Piver II). In the IIA1 stage, the vaginal resection margin must be free of tumour.

Radical hysterectomy with parametrial resection according to Querleu Type C or Piver III (Figure 2) is recommended in Stage IB2 and IIA2 after negative lymph node staging. The lymphadenectomy should be started at the inferior mesenteric artery. If these inframesenteric lymph nodes are positive, the infrarenal para-aortic lymph nodes should be removed and the operation should be stopped. If lymphadenectomy is negative, the radical hysterectomy procedure starts by dissecting the uterine vessels at their origin from the internal iliac vessels, ureteral preparation is performed down to the bladder, sacrouterine and cardinal ligaments are dissected at the sacrum and pelvic wall, and a vaginal cuff is resected.

An indicated lymphadenectomy contributes considerably to the morbidity of the surgery. Therefore, efforts have been made to replace systematic lymphadenectomy with a sentinel approach. Results of several studies indicate that sentinel lymphadenectomy offers a feasible and reliable alternative in patients with a tumour size <2 cm.[14,15] If technetium and blue staining techniques are combined then the sensitivity reaches 93.5%, with a negative predictive value of 99.1%. A Cochrane analysis of 20 studies revealed a sensitivity of 92% and detection rate of 97%. False-negative rates can be further minimised using bilateral sentinel resection and immunohistological ultrastaging.[16] However, because the data derive from retrospective analyses and oncological parameters, the sentinel concept cannot yet be regarded as a clinical standard.[3]

In cases with positive pelvic lymph nodes, and irrespective of the clinical stage, the operative concept is abandoned in favour of radiochemotherapy. Fertility may be preserved by trachelectomy in selected Stage IA/B patients without lymph node involvement,[2,3] and eventually be followed by secondary hysterectomy after accomplishment of pregancy. In Stage IA without lymphangiosis, an *in sano* conisation will probably lead to comparable results with lower morbidity.[12,17,18] Ovaries may be preserved in most premenopausal patients by ovariopexy, although ovariectomy may be necessary in some patients with adenocarcinoma.[3] Adnexectomy should be the procedure in postmenopausal patients with macroinvasive CVC.

THE ROLE OF LAPAROSCOPY

Laparoscopic treatment of early CVC follows the stage-dependent recommendations described above and therefore represents a variation of access rather than a different oncological concept.

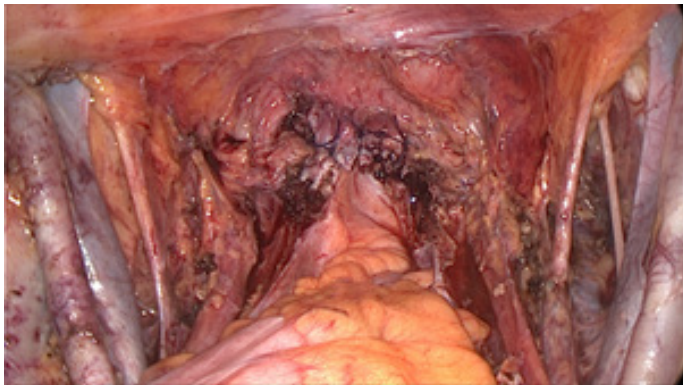

Figure 2: Operative result after total laparoscopic radical hysterectomy with parametrial resection according to Piver III (cervical carcinoma IB2).

The minimally invasive approach, however, promises significant reduction of surgery-induced morbidity when compared with the classical open abdominal procedure.

Safety and Feasibility

Numerous reports have proven both the feasibility and favourable outcome of laparoscopic radical hysterectomy (LRH) and lymphadenectomy in early CVC (Table 1). Most studies refer to Stages IA2 and IB1, but laparoscopy can also be successfully used in higher stages if operative therapy is indicated.[19-34] Conversions to laparotomy are rarely necessary. The minimally invasive procedures tend to last longer than open surgery, with median time differences ranging from 5-76 minutes in the different series, although median overall operating times show a broad range between 92 and 371 minutes. Median blood loss is reported to be between 55-450 ml, which is significantly less than that of open surgery in almost all reported series. Only robotic radical hysterectomy resulted in even lower amounts of bleeding, and this was only in one study.[28] Hospital stay was significantly shorter in all series and decreased to only 2 days in one report.[23] Intra and postoperative complications occurred in approximately 6-10% but did not differ significantly from the open abdominal approach. These complications consisted of problems relating directly to the procedure, such as bleeding or cystotomy, and problems relating to more general events, such as embolism or infections. Long-term complications such as bladder/rectal dysfunction, ureteral stenosis, or fistula occurred in approximately 10% of both laparoscopic and open abdominal cases. Thus, available feasibility data on the laparoscopic approach to early CVC surgery reveal longer durations of the procedures but better short-time outcome with less blood loss, fewer transfusions, shorter hospitalisation, and no increase in complication rates in comparison with open abdominal access.

Oncological Radicality

Oncological radicality has been evaluated considering the number of resected lymph nodes during indicated pelvic lymphadenectomies, as well as the status of vaginal and parametrial resection margins.[19-24,26-30,33,35] Median numbers of resected lymph nodes ranged between 11 and 31, which did not differ from open pelvic lymphadenectomy results. In his large series of 248 patients, Puntambekar et al.[21] reported a median lymph node number of 18. The lowest individual numbers were 9-12, and the highest were 39-61. Remarkable ranges such as 10-61[22] and 12-34[28] may indicate that individual factors beyond surgical radicality or type of surgical access influence the result of lymph node counts. Tumour-free parametrial resection was also generally reported, although most studies dealt with early stages in which parametrial involvement was not to be expected. There are limitations to the existing literature, particularly regarding the results of treating IB2 tumours, and many of the published case series lack data on pathology characteristics and immediate and late outcomes.

While most series were either retrospective or included comparisons with historical controls, the studies by Naik et al.[36] and Simsek et al.[37] concern randomised controlled designs. However, Naik et al.[36] compared laparoscopically assisted radical vaginal but not total laparoscopic hysterectomy with abdominal radical hysterectomy. In this setting there was a clinical short-term advantage confirmed in the laparoscopically assisted treatment group, but surgical radicality was found to be inferior, with smaller vaginal resection margins (1.26 cm versus 2.16 cm) and shorter parametria (1.3 cm versus 2.79 cm). No data on the clinical significance of these findings were reported. Simsek et al.[37] randomised 88 patients to either total laparoscopic (n=35) or open surgery (n=53) and did not find differences concerning the number of resected lymph nodes or tumour-free resection margins. Complete tumour-free resection was also achieved in all cases with parametrial infiltration, which was found in 11.4% of

the laparoscopically treated patients and in 16.9% of the open surgery group.

Oncological Results

Recurrence and survival data are available from few studies (Table 2). Most series focus more on technical feasibility than on oncological outcome, and follow-up times are short. A low recurrence rate of 2.8% after total LRH in Stages IA2-IB1 was reported by Puntambekar et al.[21] in a large series of 248 patients after a median follow-up period of 36 months. Toptas and Simsek[35] found 13.6%, although the number of patients treated was small (22 individuals of whom 3 relapsed after a median follow-up of 42.5 months). Park et al.[29] reported a 5-year recurrence rate of 22% in larger tumours of Stages IB2-IIA2, and Chen et al.[24] found 16.3% after a median follow-up of 36.45 months (range: 8-76) for Stages IA-IIIB. A matched-pairs analysis of 263 patients undergoing LRH versus the same number of patients undergoing an open technique by Nam et al.[27] revealed no higher risk of recurrence (hazard ratio [HR]: 1.28, 95% confidence interval [CI]: 0.62-2.64) or death (HR: 1.46, 95% CI: 0.62-3.43). Even in patients with tumours >2 cm, the HRs were 0.82 (95% CI: 0.31-2.16) and 1.01 (95% CI: 0.35-2.95), respectively, and 5-year recurrence-free survival rates did not significantly differ (92.8% versus 94.4%).

A recently published study by Ditto et al.[34] compared 60 prospective patients undergoing LRH with 60 matched patients undergoing open procedures. As part of favourable feasibility data, the study showed that the execution of LRH or radical abdominal hysterectomy did not influence the site of recurrence (p>0.2) or survival outcomes in terms of the rates of 5-year disease-free survival (p=0.29, log-rank test) and overall survival (p=0.50, log-rank test).

Table 1: Feasibility data on total laparoscopic radical hysterectomy for early cervical cancer.

Study	N	Clinical stage	Conversion to laparotomy, n	Median operating time, min (range)	Median blood loss, ml (range)	Blood transfusion, n	Short-term complications, n	Long-term complications, n
Abu-Rustum et al.[19]	19	IA2-IB1	2	371 (230-600)	301 (75-1,500)	n.r.	2 (bleeding, cystotomy)	n.r.
Ramirez et al.[20]	20	IA2-IB1	0	n.r.	200 (25-700)	1	3 (cystotomy, pulmonary embolus, pneumomediastinum)	2
Puntambekar et al.[21]	248	IA2-IB1	0	92 (65-120)	165	n.r.	15	17
Zakashansky et al.[22]	30	n.r.	0	318.5 (200-464)	200 (100-600)	0	n.r.	n.r.
Frumovitz et al.[23]	35	IA2-IB1	n.r.	344	319	4	6 (postoperative infection)	n.r.
Chen et al.[24]	295	IA-IIIB	5	162 (110-350)	230 (50-1,200)	n.r.	12	31
Malzoni et al.[25]	65	IA1-IB1	n.r.	196 (182-240)	55 (30-80)	n.r.	n.r.	n.r.
Taylor et al.[26]	9	IA2-IB1	n.r.	231.7	161.1	0	0	n.r.
Nam et al.[27]	263	IA2-IIA	n.r.	n.r.	379.6	n.r.	18	24
Chong et al.[28]	50	n.r.	0	211.2 (164-258)	201.9 (53-350)	4	4	n.r.
Park et al.[29]	115	IB2-IIA2	2	n.r.	n.r.	n.r.	n.r.	n.r.
Kong et al.[30]	40	IB-IIA	n.r.	254.5	449.1	n.r.	n.r.	n.r.
Bogani et al.[31]	65	n.r.	2	245	200	4	4	n.r.

n.r.: not reported.

Table 2: Comparative study results of total laparoscopic radical hysterectomy (TLRH) versus open abdominal radical hysterectomy (ARH) and robotic radical hysterectomy (RRH) for early cervical cancer.

Study	Design	TLRH, n	Comparator procedure, n	Median operating time: TLRH vs comparator, min	Median blood loss: TLRH vs comparator, ml	Mean length of hospital stay: TLRH vs comparator, days	Mean number of pelvic lymph nodes removed: TLRH vs comparator, n	Disease-free survival: TLRH vs comparator, %
Abu-Rustum et al.[19]	Retrospective, cohort study	19	195 (ARH)	371 vs 295 (p<0.01)	301 vs 693 (p<0.01)	4.5 vs 9.7 (p<0.01)	25.5 vs n.r.	100 vs n.r.
Zakashansky et al.[22]	Prospective, case-controlled	30	30 (ARH)	318.5 vs 242.5 (p<0.01)	200 vs 520 (p<0.01)	3.8 vs 5.6 (p<0.01)	31 vs 21.8 (p<0.01)	100 vs n.r.
Frumovitz et al.[23]	Retrospective	35	54 (ARH)	344 vs 307 (p=0.03)	319 vs 548 (p=0.009)	2 vs 5 (p<0.001)	14 vs 19 (p=0.001)	n.r.
Nezhat et al.[38]	Prospective, non-randomised	30	13 (RRH)	323 vs 318 (n.s.)	157 vs 200 (n.s.)	2.7 vs 3.8 (n.s.)	25 vs 31 (n.s.)	100 vs 100 (n.s.)
Malzoni et al.[25]	Retrospective	65	62 (ARH)	196 vs 152 (p<0.01)	55 vs 145 (p<0.01)	4 vs 7 (p<0.01)	n.r.	n.s.
Taylor et al.[26]	Retrospective, matched controls 2:1	9	18 (ARH)	231.7 vs 207.2 (n.s.)	161.1 vs 394.4 (p=0.059)	2.9 vs 5.5 (p=0.012)	n.r.	100 vs 100 (n.s.)
Nam et al.[27]	Matched pairs	263	263 (ARH)	n.r.	379.6 vs 541.1 (p<0.001)	12.5 vs 20.3 (p<0.001)	33.6 vs 29.1 (p<0.001)	92.8 vs 94.4 (n.s.)
Chong et al.[28]	Prospective, non-randomised	50	50 (RRH)	211.2 vs 230.1 (p=0.025)	201.9 vs 54.9 (p<0.001)	n.r.	23.1 vs 25 (n.s.)	n.r.
Park et al.[29]	Retrospective	115	188 (ARH)	n.r.	Significantly less in TLRH group (p=0.003)	Significantly shorter in TLRH group (p<0.001)	n.r.	78 vs 77 (n.s.)
Kong et al.[30]	Retrospective	40	48 (ARH)	254.5 vs 246 (n.s.)	449.1 vs 588 (p<0.001)	14.8 vs 18 (p=0.044)	n.r.	97.5 vs 97.9 (n.s.)
Bogani et al.[31]	Prospective, case-controlled	65	65 (ARH)	245 vs 259.5 (n.s.)	200 vs 500 (p<0.001)	4 vs 8 (p<0.001)	n.r.	n.s.
Toptas et al.[35]	Retrospective	22	46 (ARH)	n.r.	n.r.	n/a	28 vs 32 (medians, n.s.)	86.1 vs 90.6 (n.s.)
Ditto et al.[34]	Prospective, propensity-matched comparison	60	60 (ARH)	215.9 vs 175.2 (p<0.001)	50 vs 200	4 vs 6 (p<0.001)	25.4 vs 34.6 (p<0.001)	n.s.

n.s.: not significant; n.r.: not reported; vs: versus

In a published series, disease-free survival rates range between 78% and 100% depending on clinical stage and follow-up, but no study revealed significant differences between laparoscopic and open (or robotically assisted) approaches.[19,22,23,25-31,35,37,38] These results were confirmed by a Health Technology Assessment report from 2010[39] and a systematic review including data from 1,339 patients in 21 studies on laparoscopic treatment.[40]

Nerve-Sparing Concept

Despite the proven advantages of minimally invasive access for CVC surgery, postoperative and long-term morbidity are considerable with regard to bladder, bowel, and sexual dysfunction due to damage of the pelvic autonomic nerves during radical hysterectomy. Nerve-sparing techniques have been introduced to preserve these structures.[41] Identification and conservation of the inferior hypogastric plexus results in significantly less bladder dysfunction and improved sexual results,[42-44] and should therefore be a mandatory approach in order to reduce surgical morbidity. Magnification during laparoscopy or robotic surgery may facilitate identification of the neural structures with measurable impact on bladder function.[45,46]

Laparoscopy in Locally Advanced Disease

Locally advanced cervical carcinoma should be treated by radiochemotherapy.[2,3] Laparoscopy can serve as a means of staging in order to define and document the spread of the disease.

Neoadjuvant chemotherapy followed by surgery is discussed as an alternative to radiochemotherapy. This may result in improved operability but positive data on progression-free and overall survival from a Cochrane analysis in 2012[47] were not reproduced by a more recent meta-analysis.[48] Therefore, recommendations restrict its use to study conditions.[3,47,48] The role of LRH was investigated in this setting compared with abdominal radical hysterectomy and found to be favorable in terms of surgical outcome, and with comparable oncological results.[49,50] Favero et al.[51] found residual disease in 9 of 33 Stage 1B2-IIB patients (27%), mostly cases of adenocarcinoma, during laparoscopic completion surgery after primary radiochemotherapy, and therefore advocated laparoscopic surgery to improve local tumour control. Further studies will define both the role of neoadjuvant regimens as well as the role of the laparoscopic approach in this framework.

Guideline Recommendations

Despite the fact that randomised data on recurrence and survival rates are lacking,[52] the available retrospective and case-controlled results on oncological outcome, together with the feasibility data decribed above, indicate the equivalence of laparoscopic and open approaches. Therefore, current guidelines such as the Scottish Intercollegiate Guidelines Network in 2008,[53] the British National Institute for Health and Clinical Excellence in 2010,[54] and the German S3-Leitlinie zur Therapie des Zervixkarzinoms in 2014,[3] as well as the National Comprehensive Cancer Network (NCCN) Guideline Cervical Cancer[2] recommend LRH in early CVC as an alternative to open radical hysterectomy.

CONCLUSION

The laparoscopic approach to early CVC treatment can be regarded as an alternative to open surgical procedures, with good clinical results as far as feasibility and safety are concerned. The minimally invasive approach may further develop using robotic-assisted surgery, which has been introduced with at least comparable results in recent pilot studies.[55] Well-known advantages of minimally invasive techniques are as relevant for oncological patients as they are for patients with benign conditions. The endoscopic procedure does not represent a new concept, but a variation in access following the same oncological principles of stage-dependent therapy as open surgery. Available data, which are mostly retrospective, confirm a reduction in short-term morbidity without loss of surgical radicality. Long-term and prospective data on recurrence rates and survival are needed. The experience and 'know-how' of the operating surgeon remain of utmost importance for surgical and oncological success.

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