Stage I ovarian cancer: Comparison of laparoscopy and laparotomy on staging and survival

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Summary

Objective: The aim of this study was to compare staging accurateness as well as survival when managing early ovarian cancers by laparoscopy or laparotomy.

Material and methods: We have conducted a retrospective and multicentric study in France. Only Stage I ovarian epithelial cancers operated on from January 1, 1985 to December 31, 1999 were taken into account. Respondents had to fill in a form detailing in each case the surgical access; the surgical acts performed during the initial intervention as well as data on the patient's follow-up. Lack of follow-up or final Stage > I were considered as exclusion criteria. Data were recorded and analysed with SPSS 7.5 and STATA (Stata statistical sofware 7.0). (ANOVA, chi-square test or Fisher's exact test and log-rank test).

Results: 105 cases were included: 14 patients were exclusively operated on by laparoscopy (group 1), 13 other patients were subjected to a conversion from laparoscopy to laparotomy (group 2) and 78 patients exclusively underwent laparotomy (group 3). Patients in group 3 were significantly more frequently postmenopausal and had larger lesions. Cyst rupture was rare during laparoscopy (21%) and the use of an endobag was achieved in only 21% of the patients in group 1. Radical treatment was significantly more frequent in group 3 when compared to group 1 (67% vs 23%, $p < 0.05$). Laparoscopy was not adequate for staging since no lymphadenectomy was carried out by this approach. However, only 27% of patients subjected to an open approach underwent lymphadenectomy and omentectomy. The outcome in terms of survival was similar in the three groups with a mean follow-up period of 1,221 days (± 832) ($p = 0.1$).

Conclusion: Laparoscopic management of early ovarian cancer is poorly efficient in staging although disease-free survival does not seem to be affected. Further evaluation of laparoscopy in this indication is needed.

Key words: Ovarian cancer; Stage I; Laparoscopy; Laparotomy; Staging; Survival.

Introduction

Laparoscopy is today the standard access for the treatment of benign ovarian cysts. This approach provides low recurrence rates (for benign non endometriotic lesions), low post-operative adhesion formation and high post-operative fertility rates for non endometriotic benign cysts [1]. Its superiority over laparotomy in terms of aesthetic results, perioperative bleeding, hospital stay and recovery is now accepted [2].

Conversely, a strong debate has arisen on the use of laparoscopy in the management of early ovarian cancer. There is no technical reason that would not allow a laparoscopic approach for initial treatment and staging of early ovarian cancers. Laparoscopic removal of ovarian masses and comprehensive staging are now theoretically feasible. Salpingo-oophorectomy hysterectomy, omentectomy, appendectomy, peritoneal washings and biopsies can be performed by a large number of surgeons. Laparoscopic pelvic and paraaortic lymphadenectomy feasibility and accuracy have also been demonstrated [3-5]. Some papers have addressed laparoscopic staging of adnexal maligancies. Querleu reported a series of nine patients with ovarian or fallopian tube malignancies that underwent a second staging by laparoscopy [3]. Pomel has described complete laparoscopic staging with lymphadenectomy in ten patients [6]. For both series, laparoscopy was adequate for staging and provided an acceptable morbidity. However, these series are small and no comparison with laparotomy was available on patient outcome and survival.

Staging of apparently early ovarian cancer is a major subject of concern since it is accepted that the initial staging is inadequate in up to 50% of patients operated on by laparotomy, with possible consequences for adjuvant therapy and patient outcome [7, 8]. The impact of laparoscopy on quality of staging had to be assessed.

Finally, specific adverse effects of CO_2 pneumoperitoneum and laparoscopic surgery have been pointed out [9-14]. Port-site metastases and peritoneal seeding have been reported in experimental studies and following laparoscopic treatment of occult ovarian cancers. However, their actual prevalence in patients with identified cancers could be lower.

The aim of the current study was to compare laparoscopy and laparotomy in the assessment of Stage I ovarian cancer by considering staging accuracy and patient survival with these two techniques.

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Material and Methods

We conducted a national retrospective survey in France. A questionnaire was mailed to every health care centre and private practitioner involved in the management of cancers. We considered cancer centres, obstetrics and gynaecologic departments of university hospitals, obstetrics and gynaecologic departments of general hospitals and private gynaecologic surgeon members of the French Society of Gynaecologic Oncology and the French National College of Obstetrics and Gynaecology. We also solicited general surgery departments and medical oncology or radiotherapy departments in the same institutions to inquire about possible unfavourable outcomes. The questionnaire focused on acts that were carried out during the initial operation: initial surgical approach, cyst puncture, cyst rupture, conservative or radical treatment, use of an endobag, associated hysterectomy; and staging comprehensiveness: peritoneal washing and biopsies, appendectomy, omentectomy, pelvic and para-aortic lymphadenectomy. For patients initially operated on by laparoscopy and who subsequently underwent a second operation, indications for the second surgery and an interval between the two operations were required. Final staging according to FIGO, ovarian cancer pathological characteristics as well as the use of adjuvant therapy and follow-up data were also recorded.

The study included patients with proven epithelial ovarian cancer going up to Stage Ic on final evaluation and who were operated on from January 1, 1985 to December 31, 1999. The diagnosis of cancer had to be made before or during the initial operation. The mailing was carried out on January 2000 allowing a reasonable follow-up period. Exclusion criteria were: borderline lesions, non epithelial tumours and an inadequate follow-up. Disease-free survival was determined as the period of time starting from initial surgery to the last physical examination or recurrence. Data were recorded and analysed with SPSS 7.5 and STATA (Stata statistical sofware 7.0). The chi square test (or Fisher's exact test when appropriate) was used for nominal variables and ANOVA for continuous variables. Survival curves were computed using the Kaplan-Meier product-limit estimate and survival curves were compared using the log-rank test. The statistical analysis was conducted by the Clinical Investigation Centre of the European Georges Pompidou Hospital.

Results

One hundred and twelve responses concerning Stage I ovarian cancers were collected. Seven cases were excluded from the study because of non epithelial pathologies or because follow-up was not adequate. One hundred and five cases were finally included in the analysis. Seventeen different centres managed these cases (1 case to 14 cases per centre with a mean of 6): five private practitioners; six general hospitals; four medical school hospitals and two cancer centres.

Fourteen patients were exclusively operated on by laparoscopy (group 1) (13%); in 13 patients (12%) a conversion from laparoscopy to laparotomy was achieved (group 2) and 78 patients underwent an initial laparotomy (group 3) (74%). Demographic and preoperative data are given in Table 1. Groups were significantly different as to menopausal status (p = 0.02) and tumour diameter (p = 0.002). Postmenopausal women were significantly more frequent in group 3 when compared to group 2 (p = 0.02). Patients initially operated on by laparoscopy presented significantly smaller tumours than those primarily operated on by laparotomy (p = 0.006) or by laparoscopy + laparotomy (p = 0.01). Preoperative CA125 was assessed in 57 to 68% of patients (not significant, NS). Mean CA125 level was not significantly different between groups. Initial surgical proceedings carried out in each group are given in Table 2. Cyst puncture was most commonly achieved in patients operated on by laparoscopy + laparotomy (23%), while it was only performed in 2% of patients exclusively undergoing laparotomy (p = 0.02). Conversely, this happening was not significantly more frequent when patients were subjected to laparoscopy alone (Group 1) when compared to laparotomy (p = 0.3). Cyst puncture prevalence was significantly more frequent during the years 1985-1994 (6/48), when compared to the years 1995-1999 (0/55) (p = 0.008). Ovarian cystectomy was the first step of the intervention in a minority of patients in each group, without a significant difference between groups (p = 0.1). Conversely, bilateral salpingo-oophorectomy was more frequently achieved in group 3 when compared to group 1 (respectively, 67% and 23%, p < 0.05). Patients undergoing conservative treatment were significantly younger (30.1 years, SD 14) than patients treated radically (52.1, SD 15) (p < 0.05). Tumour perioperative rupture occurred in 21% of group 1 patients, 15% of group 2 and 9% of group 3 patients

Table 1. — *Patient and lesion characteristics.*

	Group 1 (14)	Group 2 (13)	Group 3 (78)	p
Age (mean, range)	46.1 (33-72)	41.9 (23-80)	52.8 (16-86)	0.056
Postmenopausal (%)	27%	23%	56%	0.02
Cyst diameter (mean, range)	85.4 (45-130)	95.7 (50-180)	138.2 (40-300)	0.002
CA125 assessment	57%	69%	68%	0.7
CA125 level (mean, range)	36 (6-100)	102 (9-337)	261 (5-3483)	0.4

Table 2. — *Initial steps of the surgery.*

	Group 1 (14)	Group 2 (13)	Group 3 (78)	p
Cyst puncture	7%	23%	2%	0.01
Cyst rupture	21%	15%	9%	0.3
Endobag	21%	7%	0	< 0.001
Cystectomy	21%	23%	7%	0.1
Bilateral salpingo-oophorectomy	23%	54%	67%	< 0.05

Table 3. — *Staging comprehensiveness.*

	Group 1 (14)	Group 2 (13)	Group 3 (78)	p
Peritoneal washings	50%	54%	60%	0.6
Contralateral adnexa	79%	77%	83%	0.1
Uterus	7%	46%	71%	< 0.001
Peritoneal biopsies	8%	23%	23%	0.4
Omentectomy	8%	38%	55%	0.01
Appendectomy	8%	0	18%	0.1
Mesentery biopsy	0	0	5%	0.4
Pelvic lymphadenectomy	0	30%	20%	0.1
Paraaortic lymphadenectomy	0	23%	27%	0.1

(NS). The use of an endobag was reported in 21% of patients undergoing laparoscopy, in 7% of patients operated on by laparoscopy + laparotomy and in none of those undergoing laparotomy ($p < 0.001$). Use of an endobag was not significantly different during the years 1985-1994 (3/48) when compared to the years 1995-1999 (1/55) ($p = 0.2$). In group 2, 50% of conversions from laparoscopy to laparotomy were motivated by the perioperative diagnosis of cancer whereas the other 50% were prompted by operative difficulties.

Staging in each group is given in Table 3. Initial staging appears to be less adequate by laparoscopy because lymphadenectomies and omentectomies are never or rarely performed. Particularly, paraaortic lymphadenectomy was never carried out in group 1, in 23% of cases in group 2 and 27% in group 3 ($p = 0.1$). However, only 27% of patients operated on by laparotomy underwent peritoneal biopsies and lymphadenectomy. Initial surgical access as well as comprehensiveness of lymphadenectomy did not differ according to the type of health care centre (Table 4).

Table 4. — *Repartition of paraaortic lymphadenectomy between types of health care providers.*

	Paraaortic lymphadenectomy
University hospital	30%
General hospital	20%
Cancer centre	18%
Private practice	22%

All patients in group 1 subsequently underwent laparotomy, which was indicated in all cases for cancer staging, whereas a smaller number of patients were re-operated in other groups for the same indication (group 2 (62% of re-operated patients), group 3 (75% of re-operated patients), $p < 0.05$). The mean period of time between laparoscopy and laparotomy was 51 days (± 12). There was no significant difference between groups for this variable ($p = 0.09$).

Final staging according to the data of the initial operation was Stage Ia ovarian cancer for most patients in each group (group 1 (50%), group 2 (60%), group 3 (69%), NS). Most tumours were of the serous type (group 1: 57%, group 2: 37%, group 3: 50%, NS). The other histologic types were distributed in accordance with classical data. Grade 3 lesions were equally distributed in the three groups: respectively 50%, 30% and 41% (NS). Platinum-based chemotherapy was not more administered in any particular group: group 1 - 14%, group 2 - 38% and group 3 - 30% ($p = 0.2$).

Length of follow-up differed significantly between the three groups ($p = 0.007$). Follow-up was significantly longer after laparoscopy + laparotomy (1,874 days ± 1,351) when compared to laparotomy alone (1,100 days ± 680) ($p = 0.001$). Conversely it was not significantly different for patients exclusively treated by laparoscopy (1,286 days ± 768) or by laparotomy ($p = 0.3$). Disease-free survival was similar for all surgical approaches (Figure 1). All patients were free of disease after

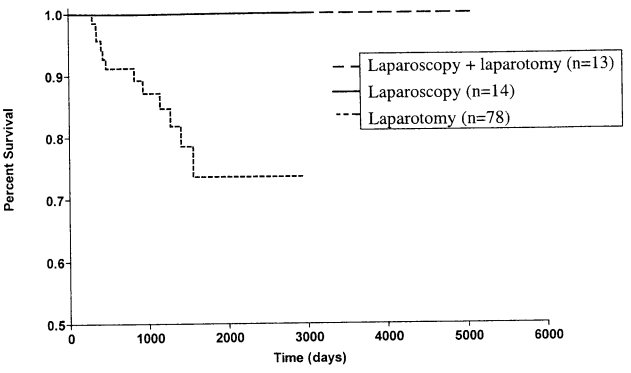

Figure 1. — Survival curves.

laparoscopy, 84% after laparotomy and 100% after laparoscopy + laparotomy (Fisher's exact test $p = 0.1$). The rate of unfavourable outcome was similar among patients who underwent paraaortic lymphadenectomy (11.5%), when compared to those who did not (12.5%, Fisher's exact test $p = 0.5$). Portsite metastasis was not recorded in this series.

Discussion

Early ovarian cancers represent less than 30% of operated ovarian cancers [15]. Some authors have already reported on the influence of laparoscopy in this situation [11-13]. However, those authors only considered the effect of laparoscopic management of adnexal masses later found to be malignant, whereas our work focuses on Stage I ovarian cancers that were known before or identified during the surgical intervention.

The first issue in this study is that laparoscopic removal of Stage I ovarian cancer appears to be acceptable. Unfavourable circumstances such as tumour puncture or rupture have only been recorded in a minority of patients. Ovarian puncture was not more frequent in patients exclusively operated on by laparoscopy when compared to those operated on by laparotomy. Moreover, the rate of cyst puncture has progressively decreased with time. In addition, tumour rupture was not favoured by the laparoscopic approach. These results are encouraging since it has been shown that perioperative tumour rupture appears to be a pronostic factor for survival in Stage I ovarian cancers [16]. Efforts should thus be made to reduce this incident and to avoid cyst puncture that may be considered as an analogous circumstance. Experimental studies as well as clinical data have ascertained the protective effect of endobags during laparoscopy on later occurrence of parietal metastases [13, 17], but this device was only used in 21% of cases in our series. The study period may explain this result to a certain extent. We report here results of patients operated on between 1985 and 1999. In the early 90's surgeons were probably less aware of the laparoscopic side-effects as well as adequate protective measures in this situation. However, we failed to find any correlation between use of bags and year of treatment. We do expect better results from an ongoing study

enrolling patients operated on after 1999. Finally, many women exclusively operated on by laparoscopy were subjected to conservative management, as we recorded a low rate of bilateral salpingo-oophorectomy and hysterectomy in this group. This may be interpreted as inadequate treatment. However, conservative treatment, aiming to preserve fertility, may also have been intentional in this group of young patients as it provides acceptable results in early ovarian cancer outcome [18, 19].

The second issue is that ovarian cancer staging was generally not adequate when patients exclusively underwent laparoscopy. Peritoneal biopsies or omentectomies were only performed in a small number of those patients, while paraaortic dissections were never carried out. This is an important issue since there is growing evidence in the literature that complete lymphadenectomy is required in apparent ovarian cancers. Burghardt *et al.* found metastatic nodes in 15 to 23% of clinical Stage I ovarian cancers [20-22]. Lymph node metastases are restricted to the pelvic area in only 25% of cases, associated with paraaortic metastases in 50% of cases and may be confined only to the paraaortic area in 25% of cases [23]. In addition, unilateral dissection may not be comprehensive enough since contralateral lymph node metastases can be observed in up to 30% of patients with carcinomas clinically confined to one single ovary [24]. Thus, laparoscopic paraaortic lymphadenectomy, and to a lesser extent pelvic lymphadenectomy appear as limiting factors for a complete surgical staging by laparoscopy. Some surgeons have reported their large experience of over 100 cases in various indications with more than 70% of procedures performed by laparoscopy [4, 5]. It appears that laparoscopic paraaortic lymphadenectomy requires a high skill in laparoscopy and is time consuming (75 to more than 300 minutes) [4, 15, 25]. This probably explains the lack of laparoscopic lymphadenectomy in our series, which was only performed by a few pioneering teams at the time of the study. Interestingly, a recent paper issued from the GOG reports that 17/57 paraaortic lymphadenectomies carried out by laparoscopy in the same period on cervical cancer patients were not complete [26]. In our study, complete surgical staging was achieved in only 27% of patients operated on by laparotomy. This is partly explained by the fact that paraaortic lymphadenectomy was not in the policy of one of the centres in our study. In fact, early ovarian cancer staging by laparotomy has previously been found to be inadequate in a significant number of cases. In the report of Young *et al.*, only 25% of patients had an adequate incision and 31% of them were finally upstaged because of positive cytology, metastatic lymph nodes or extension to the pelvic peritoneum [7]. Other papers on this topic are in agreement with this report, providing evidence that the surgeon's ability to carry out lymphadenectomy may probably be as important as the surgical approach itself [27, 28].

However, comprehensive surgical staging has an important role in the prognosis of early ovarian cancers as it gives more reliable indications for adjuvant therapy [8, 29, 30]. Laparoscopic restaging appears interesting because patients are then referred to centres specialised in oncology as well as laparoscopy. In this setting, Le Blanc *et al.* staged 28 patients and upstaged six of them. One laparotomy was required because of dense adhesions and no serious complications occurred in this series. Evolution was favourable for 21/22 of Stage Ia ovarian cancers [15]. Childers *et al.* restaged 14 patients with clinical Stage I ovarian tumours and eight of them were upstaged. Two complications were recorded: a vena cava injury and an abdominal wall hematoma [25]. Retroperitoneal vessel injuries, which occurred in 5% of patients, appear as the major risk of this operation. Pomel *et al.* restaged ten patients and upstaged one of them. They reported a mean operative duration of five hours. Two major complications were recorded: a hemoperitoneum which required laparotomy and a pulmonary embolism [6].

The third issue of this study is that survival is in agreement with published data in spite of earlier discussed limitations. Stage I ovarian cancer 5-year survival rates ordinarily range from 75 to 95% [29-32]. Since this stage represents the only curable situation, it should be advisable to attain the highest survival rate no matter what surgical access is adopted. Our results are reassuring since patients operated on by laparoscopy or laparotomy presented similar outcomes. In addition, no adverse event was recorded after laparoscopy. In a recent paper reviewing early ovarian cancer prognostic factors, Vergote *et al.* showed that the strongest determinant aspects were tumour differentiation and preoperative rupture [16]. None of these factors are influenced by laparoscopy. Perioperative rupture may also be a determinant, but our study failed to reveal any evidence of this, probably because it happened in a minority of patients. Our results are convergent with those arising from experimental studies showing that survival is similar after CO_2 pneumoperitoneum or laparotomy [33].

The specific impact of laparoscopy on tumour dissemination and growth has to be discussed. Peritoneal dissemination of tumour cells could be enhanced by CO_2 pneumoperitoneum, as demonstrated by animal studies [9]. In humans, Lehner *et al.* reported a prognosis that was worsened when patients were re-operated on more than 17 days after laparoscopy [10]. This was not revealed in our study probably because it only included patients with early ovarian cancer on final evaluation. Some other papers reported that an inadequate management of ovarian cysts later found to be malignant was responsible for port-site metastases and peritoneal seeding [11-14]. We did not record any of these complications in our survey. However, in these last series ovarian cancers were generally not previously apprehended so that some technical or oncological inaccuracies might have occurred during the laparoscopic procedure and would partly explain the poor outcome. The surgeons' learning curve in oncologic surgery should also be taken into account as has been demonstrated for lymphadenectomy [34]. Adverse events are infrequent when oncologic constraints are respected. In one series con-

cerning laparoscopic management of 138 suspect pelvic masses, Childers *et al.* reported seven (out of 14) disclosed cancers that were exclusively staged and treated by laparoscopy. In another series, the same authors gave an account of low-rate port-site metastases (< 1% of patients) [35]. It should be emphasised that these issues arise from a skilled surgical team that is highly experienced in oncologic surgery as well as laparoscopic surgery.

Nevertheless, the risk of bias should not be overlooked in our series. The most important bias would be an underestimation of patients with poor outcomes since some of them may have been lost in this study. No register for this disease is available in France and we cannot compare our data with others. The second bias may arise from patient heterogeneity in the three groups; clinical presentations in group 3 being the most severe. Finally, power calculation shows that 80 patients per group are necessary to disclose a survival difference of 10% (alpha = 5%, power = 90%, 5-year survival = 95%). All this has led us to conduct a second more appropriate survey that includes Stage I ovarian cancers operated on after the year 1999.

Finally, the current study shows that early ovarian cancer can be removed laparoscopically with a limited number of inadequate acts. Laparoscopy was particularly inadequate for retroperitoneal staging during the years 1985-1999, but laparotomy did not provide better results. Laparoscopy could be of interest for restaging in referral centres.

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PUBLISHED AND FORTHCOMING CHAPTERS

Published Chapters

1) Hormone replacement therapy (HRT) and cancer. 2) Techniques of urinary diversion in Gynecologic Oncology. 3) Granulosa cell tumors of the ovary. 4) Genetics for Gynecologic Oncologists. 5) Endodermal sinus tumors (yolk sac tumors) of the ovary. 6) The parametrium and paracolpium – an anatomic and surgical symposium with emphasis on the cardinal ligament as it relates to radical hysterectomy. 7) Malignant melanoma of the vulva. 8) Paclitaxel in breast cancer and gynaecological tumours. 9) Current status of intraperitoneal chemotherapy in the management of epithelial ovarian carcinoma. 10) Teratomas of the ovary. 11) The role of neoadjuvant chemotherapy in treating patients with carcinoma of the uterine cervix. 12) FIGO Stage IIb carcinoma of the uterine cervix. 13) Prognostic factors in epithelial ovarian cancer. 14) Global challenge of cervical cancer screening and prevention. 15) Paraaortic nodes: involvement in gynecologic malignancies. 16) New techniques and assessment of gynaecological tumours. 17) Guidelines from the biomed 2 familial breast cancer demonstration project. "Audit of a new development in medical practice in European Centres". 18) Cytotoxic drug therapy in Gynaecological Oncology: principles and practice. 19) Prognostic factors in cervical carcinoma. 20) The place of laparoscopy in the management of Gynecologic malignancies. 21) Controversies and new trends in FIGO staging. 22) Urinary function in relation to and following treatment of Gynaecological malignancies. 23) Sertoli-Leydig cell tumors of the ovary. 24) Elements of bowel surgery as it pertains to Gynecologic Oncology. 25) Principles of the perioperative management in Gynaecological Oncology. 26) Embryonal carcinoma of the ovary. 27) Endometriosis and cancer risk. 28) Fertility preservation and cancer treatments. 29) Pseudomyxoma peritonei. 30) Steroid (lipid) cell tumours of the ovary.

Forthcoming Chapters

• How to prevent and manage bleeding during and following pelvic surgery. • Gonadoblastoma of the ovary. • Anticancer vaccination in Gynecologic Oncology. • Metastatic tumours of the ovaries. • Fertility drugs, in vitro fertilisation and the risk of gynaecological malignancies. • Gynecologic Oncology protocols: endometrial cancer. • Vulvar dystrophy.

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The CME Journal of Gynecologic Oncology focuses on controversial issues and new developments in gynecologic oncology with the aim of providing a unique opportunity for those interested in subspecialty training and postgraduate education in gynecologic oncology. The journal is not a venue for original articles, but contains chapters each devoted to a single topic addressed by several internationally acknowledged, exclusively invited experts and edited by an individual distinguished in the field. Practical conclusions and guidelines are given by the Chapter Editor. News, comments, critiques, book reviews and letters are also provided.

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