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Laparoscopic hysterectomy after concurrent radiochemotherapy in locally advanced cervical cancer compared to laparotomy: a multi institutional prospective pilot study of cost, surgical outcome and quality of life

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5 study of cost, surgical outcome and quality of life.6 • **Author list and affiliations:**7 S. BAFFERT, (1), S. ALRAN (2), V. FOURCHOTTE (2), M.A. TRAORE (1), C. SIMONDI (3),
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35 The authors report no conflict of interest.

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16 All authors made substantial contributions to the concept and design or analysis and
17 interpretation of the data. All authors participated in drafting and reviewing the manuscript.

18

1 • **Abstract**

2 **Objective:** Laparoscopy allows hysterectomies after chemoradiation to be performed
3 without opening the abdominal wall. We measured the costs and quality of life for locally
4 advanced cervical cancer patients operated on via laparoscopy compared to laparotomy.

5 **Study design:** We conducted an observational prospective multicenter study on locally
6 advanced cervical cancer patients undergoing an extrafascial hysterectomy after concurrent
7 chemoradiotherapy (CRT). We assessed the costs from the medical visit before surgery up
8 to the first month after surgery from the providers' perspective and measured the quality of
9 life using the EORTC QLQ-C30 and QLQ-CX24 up to six months.

10 **Results:** 62 patients (39 laparoscopy and 23 laparotomy) from December 2008 to November
11 2011 were included. There was no difference in operative time, or intraoperative and
12 postoperative complication rates between the two groups. Intraoperative transfusion and
13 abdominal drain were significantly lower in the laparoscopy group (respectively, $p=0.04$ and
14 $p<0.01$), as well as the duration of hospital stay (7.3 d vs 5.7 d, $p<0.001$). All patients who
15 underwent laparoscopic hysterectomy were discharged to home, whereas 4 laparotomy
16 patients used convalescence homes ($p=0.01$). Mean costs at one month were €10,991 for
17 laparotomy and €11,267 for laparoscopy ($p=0.76$). Sexual activity is better for the
18 laparoscopy group at six months ($p=0.01$).

19 **Conclusion:** Laparoscopy for an extrafascial hysterectomy after CRT in locally advanced
20 cervical cancer patients brought better quality of life with similar costs compared to
21 laparotomy, and should therefore be the first choice for surgeons.

22

23 • **Key words:** Advanced cervical cancer, cost comparison, laparotomy, laparoscopy,
24 quality of life, laparoscopic hysterectomy

1 Introduction

2 Cervical cancer is the second most frequent cancer in women, with approximately 500,000
3 new cases diagnosed, and 270,000 deaths annually worldwide¹⁻². Although the incidence of
4 cervical cancer has decreased in industrialized countries because of screening programs and
5 progress in management of intraepithelial lesions, 60% of cases are at advanced stages at
6 diagnosis. In France, the estimation of new cases in 2015 is 3,060, with the highest incidence
7 among women in their 40s, leading to nearly 1,070 deaths and a 5-year survival rate of 17.2%
8 in advanced stages³⁻⁴.

9 The gold standard for treating patients with locally advanced cervical cancer (LACC) is
10 concurrent chemoradiotherapy with or without brachytherapy (CRT)⁵⁻⁶. Significant survival
11 advantages of chemoradiation in cases of LACC, have been demonstrated in a meta-analysis⁷.

12 The value of completion surgery after CRT in LACC however, still remains debatable⁸⁻¹¹, and
13 few studies are available¹²⁻¹³. Furthermore, hysterectomy after CRT remains a questionable
14 treatment option, in particular in cases of partial response. Results from multicenter studies
15 have demonstrated that residual disease after concurrent chemoradiation therapy and
16 brachytherapy impact on disease free survival¹⁴⁻¹⁶. Because the accuracy of imaging
17 techniques are not sufficient to measure residual disease¹⁷⁻¹⁸, surgery remains the current
18 practice in many countries. Furthermore, completion surgery reduces residual pathological
19 disease, which represents an important prognostic factor¹⁹⁻²³.

20 We previously assessed the consequences of hysterectomy by laparotomy after CRT and
21 brachytherapy, and showed a high rate of grade 2/3 morbidity (26%), particularly due to
22 urinary complications¹⁴. The feasibility and consequences of laparoscopic hysterectomy after
23 RCT for LACC have not been sufficiently assessed. In a retrospective series of 102 patients,
24 Colombo et al²⁴. studied 56 laparoscopic hysterectomies over a period of 8 years. The

1 question arises as to whether this intervention improves the quality of life of these patients,
2 and the efficiency cost and surgical outcome. A comparison of laparoscopy to laparotomy in
3 terms of surgical outcome, cost and quality of life has not been prospectively assessed in the
4 context of surgery after CRT in LACC. The treatment of cervical cancer is expensive and is
5 estimated to total 44 million Euros annually in France, corresponding to a mean patient cost
6 of €22,697 for stage III to €6,886 for stage V disease²⁵.

7 Our study was aimed at assessing the benefit of laparoscopy, in terms of cost, surgical
8 outcome and quality of life.

9

10 **Materials and methods**

11 *Study design and patient details*

12 Between December 2008 and November 2011, 62 consecutive patients (39 laparoscopy and
13 23 laparotomy) from 13 French institutions were included in a prospective multicenter
14 comparative observational non-randomized study.

15 Inclusion criteria were invasive cervical cancer proven by a core biopsy before treatment,
16 stage IB2, and IIA, IIB (proximal), M0, preoperative external platinum based
17 radiochemotherapy, +/- utero-vaginal brachytherapy, and extrafascial hysterectomy (+/-
18 lymphadenectomy, pelvic and latero aortic), via laparoscopy or laparotomy, with the
19 feasibility of a one year follow-up. The choice of the surgical approach was at the discretion
20 of the surgeon. Each surgeon used one of the two techniques. Surgeons trained in laparoscopy
21 performed laparoscopic extrafascial hysterectomy, plus lymphadenectomy, whilst surgeons
22 less trained in laparoscopy performed these procedure by laparotomy. Observational study is
23 more suitable to capture current practice in a real-world situation.

1 Hysterectomy was proposed in cases when tumor residual at the end of the treatment was
2 suspected.

3 Initial staging was defined according to the International Federation of Gynecology and
4 Obstetrics (FIGO) staging system. Staging was performed using a clinical pelvic examination,
5 Magnetic Resonance Imaging (MRI), and Computed Tomography (CT).

6 *Treatment:*

7 All patients received radiochemotherapy. Concomitant Cisplatin (CDDP) was given on the
8 first day of each week of radiotherapy. Laparoscopic surgical staging of lymph node
9 involvement, pelvic and/or aortic, was initially undertaken to set the field of external
10 radiotherapy in some teams, in others it was a radiological stadification. Radiation therapy
11 was administered at 1.8 Gy in 22 to 25 fractions according to international
12 recommendations²⁶.

13 Surgery consisted of an extrafascial hysterectomy. Patients undergoing a laparoscopy were
14 positioned in the Trendelenburg position, and a 0°-laparoscope (10-mm umbilicus trocar) and
15 three 5-mm trocars (left and right iliac fossa and upper pubic region) were inserted. The
16 abdominal pressure was maintained at 12 mm Hg. Laparotomies were performed using a
17 Pfannenstiel transverse incision or a midline incision.

18 Post-operative follow-up occurred from surgery to one month later, and included the hospital
19 stay, and a first post-operative visit.

20 *Studied parameters*

21 Studied parameters were baseline demographic information (age, Performance Status Score,
22 Body Mass Index), tumor characteristic (histology, initial tumor size determined clinically
23 and by MRI before initiation of treatment, FIGO staging, nodal disease status), preoperative
24 treatments (surgery for node staging, CRT, radiotherapy, brachytherapy), treatment response

1 (pathological results, tumor size) and complications according to the Chassagne glossary²⁷.
2 Economic data included the treatment modality, resources consumed, including mean
3 personnel time, conversion to laparotomy and its causes, hospitalization, complications, and
4 annual follow-up. We used the cancer QLQ-C30 version 3.0 from EORTC which is a quality
5 of life instrument for use in international clinical trial in oncology and the EORTC QLQ-
6 CX24 module which is dedicated to patients with cervical cancer and validated by the
7 European Organization for research and Treatment of cancer. Quality of life was evaluated
8 using a patient self-completed survey sent by post at four time periods, before surgery (T0),
9 one week after surgery at the first visit (T1), and one (T2) and six months post-surgery
10 (T3))²⁸⁻²⁹. Questionnaires were sent by prepaid envelopes to the Institut Curie (within 8 days
11 with respect to T1, T2, or T3).

12 This study contained no modifications of standard practice in each institution, and informed
13 consent was not required. It was approved by the regional ethical committee (Authorization n°
14 908075).

15 *Economic assessment*

16 We conducted our analysis from the hospital provider's perspective. The direct costs
17 associated with surgical strategies (laparoscopy or laparotomy) were taken into account in a
18 prospective manner, from the medical visit prior to surgery up to the first month after surgery
19 using unit costs. Costs of complications during hospitalization, costs of re-intervention for
20 complications, and costs associated with longer hospitalization were also considered. The
21 time period covered, 30 +/-5 days from surgery, allowed all important and relevant
22 consequences and costs between two strategies to be measured and compared. Cost
23 computation focused on inpatient follow-up care and the rehabilitation unit. The hospital
24 provider perspectives included hospital stay in the Medicine, Surgery, Obstetrics (MSO) unit

1 and follow-up care in the rehabilitation unit. In France, hospital care settings include
2 conventional hospital in charge of an MSO, post-acute care and convalescence homing.
3 Hospital provider perspectives include the hospital care setting in a global care pathway.
4 Cost calculations were made with the micro-costing method obtained from detailed
5 observations, for all patients included in the study and quantities of consumable resources.
6 The following consumable resources, linked to surgery, are counted and quantified for each
7 patient, from economic items integrated into the case report form, and per center through the
8 center survey as specific devices and annual activities. Direct costs include different surgery
9 techniques, pathology requirements, supplies, depreciation for equipment, hospital stay,
10 medical visits and surgical costs. Depreciation of the laparoscopic video System is included in
11 the direct costs, and is proportional to the time of use in surgery. Depreciation costs were
12 calculated based on a five-year straight-line depreciation. Costs are presented in Euros in
13 2010. A sensitivity analysis was performed to assess the potential effects of uncertainty
14 inherent in the study.

15 *Statistical analysis*

16 Cost comparisons were measured using a student's t-test, a Mann-Whitney test or an analysis
17 of variance (ANOVA), and are reported as the mean \pm standard deviation. Tests for
18 normality were carried out using a Kolmogorov-Smirnov test. Socio-demographic
19 characteristics, clinical information and all categorical variables were compared using a Chi-
20 square test or a Fisher's exact test. All tests were two-sided with a significant level of 5%.
21 Data was analyzed using the SAS system software (version 9.2, SAS Institute Inc.).

22 **Results**

23 A flow chart of the study population is shown in Figure 1. Patient characteristics are presented
24 in Table 1. The two groups were not statistically different except for cancer staging (FIGO)

1 and previous surgical histories. Patients in the laparotomy group had a more locally advanced
2 disease and more previous abdominal surgery. Pathological results are presented in Table 2.

3 *Preoperative treatment*

4 Twenty-two patients in the laparotomy group (95.6%) and 38 patients in the laparoscopy
5 group (95%) underwent brachytherapy. Completion radiotherapy after surgery was carried out
6 for only one patient in each group and was related to residual lymph node disease.
7 Complications related to pretreatment were the same in the two groups (7/23 (30.4%) in
8 laparotomy vs 12/39 (30.7%) in laparoscopy, $p=1.00$).

9 *Surgery*

10 Surgical characteristics are summarized in Table 3. Intraoperative transfusion was significantly
11 lower in the laparoscopy group ($p=0.04$). Similarly, abdominal drain was significantly lower
12 in the laparoscopy group compared to the laparotomy group (78.3% vs. 7.5%, $p<0.001$).
13 Urinary catheterization did not differ between the two groups (23/23 vs 38/39, $p=1.00$) like
14 duration of urinary catheterization (4.5 ± 1.4 d vs 3.9 ± 1.9 d, $p=0.07$). The time between the
15 end of prior therapy and the surgery is on average within 6 to 8 weeks.

16 Although the length of induction of anesthesia as well as the length of incision was
17 significantly higher in the laparoscopy group (respectively, 37.6 min vs 29.4 min, $p=0.03$ and
18 168 min vs 210 min, $p=0.04$), the overall mean operative time did not differ significantly
19 between the two groups (258 min vs. 294 min, $p=0.06$) (Table 3). In the laparoscopy group,
20 three patients (3/39, 7.5%) had to be switched to the laparotomy group due to technical
21 requirements, and all three had a previous history of abdominal surgery and brachytherapy
22 before hysterectomy.

23 Intraoperative and postoperative complications are detailed in Table 4. Complications leading
24 to re-hospitalization and/or re-intervention are presented in Table 5. Two patients in the

1 laparoscopic group required re-operation for post-operative intraperitoneal abscesses and
2 post-operative bowel obstruction secondary to adhesion. There were no post-operative deaths
3 within 30 days after surgery in either group.

4 *Cost at one-month*

5 Resources used for each phase of the procedures are presented in Table 5, and detailed costs
6 in Table 6. The direct cost of each procedure was not statistically different at one month:
7 €10,991 ($\sigma=3616$) for laparotomy versus €11,267 ($\sigma=4237$) for laparoscopy, $p=0.76$.

8 Hospital stays for patients were significantly lower in the laparoscopy group (8.3 d vs 6.7 d,
9 $p<0.001$). Post-hospital stay in a convalescence home was required for 17.4% (4/23) of the
10 patients after laparotomy (21, 23, 24 and 30 days respectively), but was not required for any
11 patients in the laparoscopy group who return home after surgery. The one-month follow-up
12 step includes the additional cost convalescence for the laparotomy group, while all patients in
13 laparoscopy group have hospital discharge at home. The one-month follow-up step results in
14 significantly lower costs for the laparoscopic group compared to the laparotomy group (€29
15 vs. €1,739, $p=0.05$).

16 The extra costs of three conversions reached €18,157 ($\sigma=€11,944$) per converted patient
17 (min=11,131, max=31,949). The difference in cost between the two procedures was not
18 significant, even if the 3 cases of conversion were not included in the analysis ($p=0.96$).

19

20 *Quality of life up to 6 months*

21 Assessment of quality of life using EORTC QLQ-C30 at one week after surgery was better
22 for patients having undergone laparoscopy compared to laparotomy. At one month, global
23 health and quality of life, physical functioning and role functioning were better in the
24 laparoscopy group (respectively $p=0.01$, $p=0.01$, $p=0.05$). At six months, the measurable

1 benefits remained for patients who underwent laparoscopy, in particular they experienced less
2 fatigue than patients who underwent laparotomy ($p=0.04$). Using the specific cervical cancer
3 questionnaire, CX24, only sexual activity was significantly better at six months for the
4 laparoscopy group ($p=0.01$).

5 **Discussion**

6 Our prospective multicenter study compared the feasibility of laparoscopic versus laparotomic
7 hysterectomy after CRT in LACC. Whilst these procedures had equal hospital costs at one
8 month, the quality of life was considerably better for the laparoscopy patients.

9 *Medical outcome and quality of life*

10 Few studies have assessed the clinical outcomes and complications of hysterectomy after
11 CRT in LACC. Colombo PE *et al.*²⁴, included 56 laparoscopy patients after RCC over a 8
12 year period, and Chereau E *et al.*⁸, studied 42 laparoscopy patients over a 10 year period.

13 Regarding complications, our study revealed no major intraoperative, early postoperative, or
14 late postoperative complications within 30 days in the two groups. In the retrospective cohort,
15 of Colombo PE *et al.*²⁴, morbidity rates and urinary complications were significantly reduced
16 in the laparoscopy group compared to the laparotomy group for radical hysterectomy and not
17 simple extrafascial hysterectomy. Other recent published studies showed total laparoscopic
18 radical surgery is feasible in patients with LACC receiving preoperative CT/RT.³⁰⁻³¹

19 As expected, from a patient perspective, hysterectomy by laparoscopy after concurrent
20 radiochemotherapy with or without brachytherapy seems to result in better quality of life
21 compared to open surgery. We measured the quality of life for a cohort of 62 patients over a
22 six-month follow-up period. Radical pelvic surgery via laparotomy and chemoradiation are
23 associated with a significant impairment of sexual function in cervical cancer patients³²⁻³³. We

1 observed a clinically relevant improvement in the overall quality of life and sexual function
2 scores which was significantly better at six months for the laparoscopy group. This
3 information can be used to guide medical decision making, and highlights that surgical
4 approaches should always be tailored to minimize the negative impact of surgery.

5 *Cost evaluation*

6 Using the *microcosting* method, our prospective series demonstrated that laparoscopy hospital
7 costs were not significantly different at one month compared to the open procedure. The
8 longer length of operating time, the costly single-use consumables, equipment and materials
9 used for laparoscopy and the extra cost of conversion (failure of laparoscopy) are offset by a
10 shorter length of stay and a reduction in the use of a convalescence home following
11 hospitalization.

12 Existing publications report heterogeneous data for the type of surgery, types of cost
13 components and inclusion criteria. No costs studies using the *microcosting* method with a one
14 month follow up after surgery have been previously reported. Dennis et al.³⁴ found that the
15 cost for radical hysterectomy was highest for robotic, followed by standard laparoscopy, and
16 lowest for laparotomy. In our study, only surgical and anesthetic instrumentations have been
17 included in the cost calculation; the cost calculation did not include staff costs, hospital stay,
18 follow-up, or resources pertaining to medical data acquisition.

19 Wright et al.³⁵ found that both laparoscopic and robotic radical hysterectomies were
20 associated with lower transfusion requirements and shorter hospital stays than abdominal
21 hysterectomy ($p < 0.05$). However, they did not use a prospective and observational design,
22 and did not report direct per-patient costs. In their study, costs were estimated using a national
23 database, which is less powerful for comparing population sub-groups or for matching
24 economic data to clinical outcomes at the individual patient level. Observational studies

1 provide accurate and detailed information on health care consumption at an individual patient
2 level. Significantly, such data allow modeling studies of healthcare costs to be refined, and
3 are critical in guiding decision-making with regard to healthcare resource allocation.

4 The length of stay for patients undergoing laparoscopy in our cohort was longer than the
5 average length reported in the literature for other countries, such as in USA for example. Bell
6 et al.³⁶ in 2008 reported an average length of stay of 2 +/- 1.2 days for laparoscopy in the
7 USA, while Lachance et al.³⁷ reported a 4 day stay for patients undergoing hysterectomy in
8 the USA. Wright et al.³⁵ reported a median length of stay of 3 days for abdominal radical
9 hysterectomy, and 2 days for laparoscopic surgery in the USA. This could be explained by the
10 differences in national health care and reimbursement systems. In the past few years, trends in
11 France are to reduce the length of stay. In France, Colombo PE et al.²⁴, reported a 5 day
12 hospital stay after laparoscopy versus 8 days for laparotomy.

13 Once the relevant range of costs has been identified, the individual items must be measured
14 and valued. The level of accuracy of cost studies is determined by the identification of cost
15 components, (gross costing and/or microcosting) and valuation of cost components (top-down
16 and/or bottom-up costing). In the *microcosting* approach, all relevant cost components are
17 defined at the most detailed level and in the bottom-up approach. Cost components are valued
18 by identifying resources used directly for a patient, resulting in patient specific unit costs.³⁶
19 Our study used the combination of *microcosting* and the bottom-up costing approach, which
20 is generally believed to be the gold standard methodology for the costing of healthcare
21 services.

22 This reporting care pathway with a one-month follow-up including transitional care such as
23 rehabilitation makes our study original and relevant. Rehabilitation care represents an
24 important potential benefit for minimally invasive surgery as it represents a large and relevant

1 cost component. Our analysis was conducted from the hospital provider perspective,
2 including inpatient hospitalization in MSO and stays in follow-up and rehabilitation care.

3 One limitation of our study is the small sample size, which is common to many similar studies
4 in this specific field. Ferrandina et al.²⁰ included 174 patients over a ten year period, Colombo
5 et al.²⁴, 102 patients over 8 years (including 56 laparoscopies), and Chereau et al.⁸ 80 patients
6 over 10 years (including 42 laparoscopies). Another limitation is that our study was non-
7 randomized. However, even if randomized studies represent the standard practice in clinical
8 research, our observational study describes current treatment in representative centers. These
9 issues had to be raised in our conclusion. Compared to previously published studies using
10 retrospective data in single institutions or databases, our study is prospective, consecutive and
11 multi institutional. We provide more comprehensive and accurate individual and primary data
12 per patient, in a setting that is relevant to current treatment protocols.

13
14 Laparoscopic radical hysterectomy after radiochemotherapy for the treatment of LACC is
15 feasible, results in lower intraoperative transfusion and abdominal drain interventions, a
16 shorter hospital stay, less convalescent time, and results in a better quality of life with similar
17 costs at one-month compared to laparotomy. For these reasons, when hysterectomy is
18 indicated for the treatment of LACC after chemoradiation and brachytherapy, the
19 laparoscopic approach must be the first choice.

20

21

22

1 References

- 2 1. Parkin DM and Bray F (2006) Chapter 2: The burden of HPV-related cancers. *Vaccine 24 S3 S11-*
3 25.
- 4 2. Munoz N, Castellsague X, de Gonzalez AB et al. (2006) Chapter 1: HPV in the etiology of human
5 cancer. *Vaccine 24 S3 S1-S10*.
- 6 3. Institut National de Veille Sanitaire. Les cancers en France en 2013. Collection état des lieux et
7 des connaissances, ouvrage collectif édité par l'INCa, Boulogne-Billancourt, janvier 2014.
8 [www.e-cancer.fr/component/.../11505-les-cancers-en-france-edition-2013]
- 9 4. Institut National de Veille Sanitaire. Données épidémiologiques sur le cancer du col de l'utérus –
10 Etat des connaissances – Actualisation 2008 – InVS.
11 [http://invs.sante.fr/publications/2008/cancer_col_uterus_2008/cancer_col_uterus_2008.pdf]
- 12 5. McNeil C. New standard of care for cervical cancer sets stage for next questions. *J Natl Cancer*
13 *Inst.* 1999;91:500-1.
- 14 6. Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin
15 versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix
16 with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology
17 Group study. *J Clin Oncol.* 1999 May;17(5):1339-48.
- 18 7. Green J, Kirwan J, Tierney J, et al. Concomitant chemotherapy and radiation therapy for cancer of
19 the uterine cervix. *Cochrane Database Syst Rev.* 2005
- 20 8. Chereau E, De La Hosserraye C, Ballester M, et al. The role of completion surgery after
21 concurrent radiochemotherapy in locally advanced stages IB2-IIB cervical cancer. *Anticancer Res.*
22 2013 ;33:1661-6.
- 23 9. Ferrandina G, Ercoli A, Fagotti A, et al. Completion surgery after concomitant chemoradiation in
24 locally advanced cervical cancer: a comprehensive analysis of pattern of postoperative
25 complications. *Ann Surg Oncol.* 2014 May;21(5):1692-9.

- 1 **10.** Sun L, Sheng X, Jiang J, et al. Surgical morbidity and oncologic results after concurrent
2 chemoradiation therapy for advanced cervical cancer. *Int J Gynecologic Obstet.* 2014
3 May;125(2):111-5.
- 4 **11.** Favero G, Pierobon J, Genta ML, et al. Laparoscopic extrafascial hysterectomy (completion
5 surgery) after primary chemoradiation in patients with locally advanced cervical cancer: technical
6 aspects and operative outcomes. *Int J Gynecol Cancer.* 2014 Mar;24(3):608-
- 7 **12.** Houvenaeghel G, Lelievre L, Gonzague-Casabianca L, et al. Long-term survival after concomitant
8 chemoradiotherapy prior to surgery in advanced cervical carcinoma. *Gynecol Oncol.* 2006
9 Feb;100(2):338-43.
- 10 **13.** Delpech Y, Haie-Meder C, Rey A, et al. Para-aortic involvement and interest of para-aortic
11 lymphadenectomy after chemoradiation therapy in patients with stage IB2 and II cervical
12 carcinoma radiologically confined to the pelvic cavity. *Ann Surg Oncol.* 2007 Nov;14(11):3223-
13 31
- 14 **14.** Classe JM, Rauch P, Rodier JF et al. Surgery after concurrent chemoradiotherapy and
15 brachytherapy for the treatment of advanced cervical cancer: morbidity and outcome: results of a
16 multicenter study of the GCCLCC (Groupe des Chirurgiens de Centre de Lutte Contre le
17 Cancer). *Gynecol Oncol.* 2006;102(3):523-9.
- 18 **15.** Hequet D, Marchand E, Place V, Fourchette V, De La Rochefordière A, Dridi S, Coutant C,
19 Lecuru F, Bats AS, Koskas M, Bretel JJ, Bricou A, Delpech Y, Barranger E. Evaluation and
20 impact of residual disease in locally advanced cervical cancer after concurrent chemoradiation
21 therapy: results of a multicenter study. *Eur J Surg Oncol.* 2013 Dec;39(12):1428-34.
- 22 **16.** Poujade O, Morice P, Rouzier R, et al. Pathologic response rate after concomitant neo-adjuvant
23 radiotherapy and chemotherapy for adenocarcinoma of the uterine cervix: a retrospective
24 multicentric study. *Int J Gynecol Cancer.* 2010 Jul;20(5):815-20
- 25 **17.** Ferrandina G, Petrillo M, Restaino G, et al. Can radicality of surgery be safely modulated on the
26 basis of MRI and PET/CT imaging in locally advanced cervical cancer patients administered
27 preoperative treatment? *Cancer.* 2012;118:392-403.

- 1 **18.** Vincens E, Balleyguier C, Rey A, et al. Accuracy of magnetic resonance imaging in predicting
2 residual disease in patients treated for stage IB2/II cervical carcinoma with chemoradiation
3 therapy : correlation of radiologic findings with surgicopathologic results. *Cancer*. 2008;113:2158
4 -65.
- 5 **19.** Fanfani F, Fagotti A, Gagliardi ML, Ferrandina G, Monterossi G, Gallotta V, Zannoni GF,
6 Scambia - Pre-hysterectomy cone biopsy is able to predict response in locally advanced cervical
7 cancer patients submitted to neo-adjuvant chemoradiation. *G. Eur J Surg Oncol*. 2013
8 Sep;39(9):1025-9
- 9 **20.** Ferrandina G, Margariti PA, Smaniotto D, et al. Long-term analysis of clinical outcome and
10 complications in locally advanced cervical cancer patients administered concomitant
11 chemoradiation followed by radical surgery. *Gynecol Oncol* 2010;119:404–40.
- 12 **21.** Jurado M, Martinez-Monge R, Garcia-Foncillas J, et al. Pilot study of concurrent cisplatin, 5-
13 fluorouracil, and external beam radiotherapy prior to radical surgery p/_ intraoperative electron
14 beam radiotherapy in locally advanced cervical cancer. *Gynecol Oncol* 1999;74:30–7.
- 15 **22.** Ferrandina G, Legge F, Fagotti A, et al. Preoperative concomitant chemoradiotherapy in locally
16 advanced cervical cancer: safety, outcome, and prognostic measures. *Gynecol Oncol*
17 2007;107:127-32.
- 18 **23.** Distefano M, Fagotti A, Ferrandina G, et al. Preoperative chemoradiotherapy in locally advanced
19 cervical cancer: long term outcome and complications. *Gynecol Oncol* 2005;99:S166–70.
- 20 **24.** Colombo PE, Bertrand MM, Gutowski M, et al. Total laparoscopic radical hysterectomy for
21 locally advanced cervical carcinoma (stages IIB, IIA and bulky stages IB) after concurrent
22 chemoradiation therapy: surgical morbidity and oncological results. *Gynecol Oncol*.
23 2009;114:404-9.
- 24 **25.** Arveux P, Bénard S, Bouée S, et al. Invasive cervical cancer treatment costs in France. *Bull*
25 *Cancer*. 2007;94(2):219-24.

- 1 **26.** Cellini N, Smaniotto D, Scambia G, et al. Chemoradiation with concomitant boost followed by
2 radical surgery in locally advanced cervical cancer: a dose-escalation study. *Am J Clin Oncol.*
3 2008;31(3):280-4.
- 4 **27.** Chassagne D, Sismondi P, Horiot JC, et al. A glossary for reporting complications of treatment in
5 gynecological cancers. *Radiother Oncol.* 1993;26:195-202.
- 6 **28.** Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and
7 Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials
8 in oncology. *J Natl Cancer* 1993. 85: 365-76
- 9 **29.** Greimel ER, Vlastic K, Waldestrom A, et al. The European Organization for Research and
10 Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Cervical Cancer Module. EORTC
11 QLQ-CX24. *Cancer* 2006;107:1812-22.
- 12 **30.** Gallotta V, Ferrandina G, Chiantera V, Fagotti A, et al. Laparoscopic Radical Hysterectomy After
13 Concomitant Chemoradiation in Locally Advanced Cervical Cancer: A Prospective Phase II
14 Study. *J Minim Invasive Gynecol.* 2015 Jul-Aug;22(5):877-83.
- 15 **31.** Gallotta V, Fanfani F, Scambia G. Minilaparoscopic nerve sparing radical hysterectomy in locally
16 advanced cervical cancer after neoadjuvant radiochemotherapy. *Gynecol Oncol.* 2014
17 Mar;132(3):758-9.
- 18 **32.** Park SY, Base DS, Nam JH, et al. Quality of Life and Sexual Problems in Disease-Free Survivors
19 of Cervical Cancer Compared with the General Population. *Cancer* 2007; 110: 2716-25.
- 20 **33.** Mantegna G, Petrillo M, Fuoco G, et al. Long-term prospective longitudinal evaluation of
21 emotional distress and quality of life in cervical cancer patients who remained disease-free 2-years
22 from diagnosis. *BMC Cancer* 2013; 18:13:127.
- 23 **34.** Dennis T, Mendonc C de, Phalippou J, et al. Study of surplus cost of robotic assistance for radical
24 hysterectomy, versus laparotomy and standard laparoscopy. *Gynecologie Obstetrique & Fertilité*
25 2012; 40:77-83
- 26 **35.** Wright JD, Herzog TJ, Neugut AI, et al. Comparative effectiveness of minimally invasive and
27 abdominal radical hysterectomy for cervical cancer. *Gynecol Oncol.* 2012 ;127(1):11-7.

- 1 **36.** Bell MC, Torgerson J, Seshadri-Kreaden U, et al. Comparison of outcomes and cost for
2 endometrial cancer staging via traditional laparotomy, standard laparoscopy and robotic
3 techniques. *Gynecol Oncol.* 2008 Dec;111(3):407-11.
- 4 **37.** Lachance J.A., Darus C.J., Stukenborg G.J., et al. A cost comparison of two strategies for treating
5 stage IB2 cervical cancer. *Int J Gynecol Cancer* 2008; 18:274–278.
- 6 **38.** Drummond M. F. *Methods for the Economic Evaluation of Health Care Programmes.* Oxford:
7 University Press; 2005.

Table 1: Characteristics of patients

	Laparotomy group (n=23)	Laparoscopic group (n=39)	P value
Age at diagnosis (yr)			
Mean \pm SD	52.2 \pm 11.0	46.6 \pm 11.4	0.1151
Performance Status Score (PSS)			
1	8 (34.8%)	20 (51%)	
2	12 (52.2%)	16 (43.5%)	0.4707
3	3 (13%)	3 (7.6%)	
Body Mass Index (BMI) (kg/m²)	24.1 \pm 4.4	23.9 \pm 5.8	0.3740
Mean \pm SD			
FIGO stage			0.0462
IB2	1 (4.3%)	10 (25.6%)	
IIA	9 (39.1%)	7 (17.9%)	
IIB proximal	13 (56.5%)	22 (56.4%)	
Tumor size, clinic (mm)			0.5785
N	19	20	
Mean \pm SD	44.7 \pm 17.2	44.2 \pm 7.2	
Tumor size, MRI (mm)			0.4462
N	20	37	
Mean \pm SD	45.1 \pm 12.8	48.1 \pm 12.5	
At least one previous history of abdominal surgery	15 (65.2%)	10 (25.64%)	0.032
Lymph node staging	14 (60.9%)	31 (79.5%)	0.0667
Clinical response	15 (65%)	24 (60%)	0.2494
MRI response (%)	16 (69%)	32 (82%)	0.6451
Complete response	10 (43.5%)	25 (64.1%)	0.1487

Categorical data N(%) statistical test is only on documented data. Non parametric tests: Wilcoxon or exact test

Table 2: Pathology results

	Laparotomy group (n=23)	Laparoscopic group (n=39)	P value
Lymphovascular invasion	2 (8.7%)	5 (12.8%)	1.0000
Free margins	21 (91.3%)	38 (97.4%)	1.0000
Missing	1	0	
No. of patients > 1 Positive pelvic lymph node involvement	17	25	0.3160
No. of patients > 1 Positive aortic lymph node involvement	3	3	1.0000
Preoperative complications N (%)	7 (30)	12 (30)	1,0000
Type of complications N (%)			0.84
chemotherapy	3 (43)	3 (25)	
radiotherapy	1 (14)	2 (17)	
surgery		3 (25)	
others	2 (29)	1 (8)	
chemotherapy and radiotherapy	1 (14)	2 (17)	
chemotherapy and surgery		1 (8)	

Categorical data N(%) statistical test is only on documented data. Non parametric tests: Wilcoxon or exact test

Table 3: Surgical characteristics

	Laparotomy group	Laparoscopic group	P value
Total hysterectomy	5 (21.7%)	8 (20%)	1.0000
Extrafascial hysterectomy	18 (78.3%)	33 (82.5%)	0.7448
Lymph node dissection	17 (73.9%)	28 (70%)	0.7811
Laparotomy incision –			
Pfannenstiel transversal	16 (69.48%)		
Midline	7 (30.43%)		
Laparoscopy	Open Laparoscopy	31 (77.50%)	
	Parietal peritoneum	9 (22.50%)	
Conversion to laparotomy*		3 (7.5%)	
Intraoperative transfusion	3 (13%)	0	0.0446
Abdominal drain	18 (78.3%)	3 (7.5%)	<.0001
Duration of abdominal drain (d) Mean ± SD	4.6 ± 1.7	6.0 ± 1.0	0.1460

Categorical data n(%) statistical test is only on documented data. Non parametric tests: Wilcoxon or exact test

**No echec pneumoperitoneum*

Table 4: Intraoperative and postoperative complications

	Laparotomy group	Laparoscopic group	P value
Intraoperative complications	2 (8.7%)	2 (5.1%)	0.6232
Urinary		2	
Vascular	1		
Heart shock	1		
Complications during hospitalization	3 (13%)	3 (7.7%)	0.6615
Digestive (Grade 1)	1		
Pain (Grade 1)		1	
Pain (Grade 2)	1	1	
Hemorrhage (Grade 2)	1		
Hemorrhage (Grade 3)		1	
Complications within 30 days	6 (26.1%)	6 (15.3%)	0.5160
Infectious (Grade 3)		1	
Digestive (Grade 2)	1		
Digestive (Grade 3)		1	
Urinary (Grade 1)		1	
Urinary (Grade 3)	1	1	
Pain (Grade 1)	1	2	
Pain (Grade 2)	2		

Hemorrhage (Grade1)	1
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Categorical data n(%) statistical test is only on documented data. Non parametric tests: Wilcoxon or exact test

Table 5: Resources used for each phase of the procedures

	Laparotomy group	Laparoscopic group	P value
Pre-operative phase			
No. of surgeon visits Mean \pm SD	3.5 \pm 1.6	2.9 \pm 1.4	0.1346
No. of anesthesia visits Mean \pm SD	2.3 \pm 0.9	2.4 \pm 1.0	0.7909
No. of other visits Mean \pm SD	5.9 \pm 5.1	4.3 \pm 4.4	0.2279
Operative phase			
Mean operative time (min) Mean \pm SD	258 \pm 66	294 \pm 90	0.0601
Length of induction (min) Mean \pm SD	29.4 \pm 14.8	37.6 \pm 14.7	0.0363
Length of incision, skin to skin (min) Mean \pm SD	168 \pm 72	210 \pm 84	0.0461
Hospitalization stay			
Hospital stay (days) Mean \pm SD	7.3 \pm 1.2	5.7 \pm 2	<.0001
Continuous care unit. N (%)	3 (13.04%)	1 (2.56%)	1.0000
Intensive care unit. N (%)	0	1 (2.5%)	
One month follow-up			
Hospital discharge. N (%)			0.0159

At home	19 (82.6%)	39 (100%)	
Convalescent home	4* (17.4%)	0	
Complications leading to rehospitalization	2** (8.7%)	3*** (7.7%)	1.0000
Duration of rehospitalization			
4 days	1	1	
10 days		1	
16 days	1		
26 days		1	
Complications leading to another intervention	0	2****	0.2934

*four patients stayed 21, 23, 24 and 30 days at a convalescent home ** Bowel distension with interaperitoneal seroma *** Functional occlusive syndrome and urinary retention **** patient 1, post operative intraperitoneal abscess; patient 2 :post operative bowel obstruction secondary to adhesion

Table 6: Comparison of costs for each phase of the procedures (Euros)

	Laparotomy group (€)	Laparoscopic group (€)	P value
Preoperative phase (1)	133.0 ± 49.0	122.1 ± 44.5	0.3486
Operative phase (2)	2 835.8 ± 585.4	5 201.4 ± 787.5	<.0001
Hospitalizations stay* (3)	6 654.3 ± 1 079.1	5 298.2 ± 1 967.2	<.0001
One-month follow-up (4)	1 739.7 ± 3 082.5	929.7 ± 3 613.9	0.0570
Total Cost (1+2+3+4)	10 991 ± 36 16.9	11 262 ± 4 293.1	0.8156

*including conventional hospitalization, continuous care unit, intensive care unit

Figure 1: Chart flow

