Results of the GYNECO 02 Study, an FNCLCC Phase III Trial Comparing Hysterectomy with No Hysterectomy in Patients with a (Clinical and Radiological) Complete Response After Chemoradiation Therapy for Stage IB2 or II Cervical Cancer

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Evaluate the therapeutic impact of hysterectomy after chemoradiation therapy in locally advanced cervical cancer.
2. Evaluate the rate of histologic residual disease in patients with complete clinical and radiologic response after chemoradiation therapy.

CME

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ABSTRACT

Background. Concomitant chemoradiation (CRT) (including brachytherapy) is considered the standard management for stage IB2 or II cervical cancer in many countries. Nevertheless, some of them discuss completion surgery (hysterectomy [HT]) after CRT. The aim of this study was to investigate the therapeutic impact of such surgery.

Methods. A randomized trial was opened in France in 2003 to evaluate the interest in HT after CRT. Inclusion criteria were: (a) stage IB2 or II cervical cancer without extrapelvic disease on conventional imaging; (b) pelvic external radiation therapy (45 Gy with or without parametrial or nodal boost) with concomitant cisplatin chemotherapy (40 mg/m² per week) followed by uterovaginal brachytherapy (15 Gy to the intermediate risk clinical target volume); and (c) complete clinical and radiological response 6–8 weeks after brachytherapy. Pa-

tients were randomized between HT (arm A) and no HT (arm B). Unfortunately this trial was closed because of poor accrual: 61 patients were enrolled (in 2003–2006) and are reported on here.

Results. Thirty one and 30 patients were enrolled, respectively, in arm A and arm B. Twelve patients recurred (five of them died): respectively, eight and four in arm A and arm B. The 3-year event-free survival rates were 72% (standard error [SE], 9%) and 89% (SE, 6%) (not significant [NS]) in arm A and arm B, respectively. The 3-year overall survival rates were 86% (SE, 6%) and 97% (SE, 3%) (NS) in arm A and arm B, respectively.

Conclusions. Results of the current trial seem to suggest that completion HT had no therapeutic impact in patients with clinical and radiological complete response after CRT (but this conclusion is limited by the lack of power). *The Oncologist* 2012;17:64–71

INTRODUCTION

Chemoradiation therapy (CRT) is considered as the standard treatment for bulky cervical cancer (stage IB2 or higher according to the Fédération Internationale de Gynécologie et d'Obstétrique [FIGO] classification) by many North American and western European teams [1, 2]. For such patients, the place and modality of completion surgery (after CRT) continue to be debated [3–11]. A trial was opened 8 years ago in France to evaluate the therapeutic impact of hysterectomy after CRT in patients with complete clinical and radiological response in this context. The results of that trial are presented here.

PATIENTS AND METHODS

Population

Patients with stage IB2 or II cervical cancer treated with CRT and brachytherapy having achieved a complete clinical and radiological response (based on magnetic resonance imaging [MRI]) were randomly assigned to undergo adjuvant hysterectomy or not.

Study Objectives

The primary objective was to evaluate the event-free survival (EFS) rate. Secondary objectives were evaluation of overall survival (OS) and morbidity.

Eligibility Criteria

Inclusion criteria were: (a) Stage IB2 or II cervical cancer (according to the 1995 FIGO classification [12]); (b) Age >18 years and <70 years; (c) Adenocarcinoma, squamous cell carcinoma, or adenosquamous subtype; (d) No extrapelvic disease on conventional imaging (abdominopelvic MRI or computed tomography [CT] scan and pelvic MRI); (e) Treatment using pelvic external radiation therapy (45–50 Gy with concomitant cisplatin chemotherapy (40 mg/m² per week); (f) Uterovaginal brachytherapy (dose, 15 Gy) following CRT; (g) Possible boost to the lateropelvic area (10–15 Gy) in cases of

parametrial involvement with insufficient regression at the time of brachytherapy or in cases of pelvic node involvement on initial imaging; and (h) Complete clinical and radiological response (based on MRI) evaluated 6–8 weeks after brachytherapy.

This trial was promoted by the Fédération Nationale des Centres de Lutte Contre le Cancer. The ethical review board gave its approval on October 2002 and the trial was opened in France in 2003. Written informed consent was obtained before entry into the study and all institutional and national regulations were fulfilled.

Study Design and Treatment

Parametrial and vaginal involvement were defined based on clinical examination. Nodes (pelvic and para-aortic) were considered “suspicious” if the size of the smallest diameter was >10 mm on conventional imaging (MRI or CT scan). Patients with suspicious para-aortic nodes on pretherapeutic conventional imaging and in whom nodal involvement was confirmed after radio-guided fine-needle aspiration were excluded. The use of positron emission tomography (PET)–CT imaging was optional in this trial. An initial laparoscopic para-aortic lymphadenectomy with or without pelvic lymphadenectomy using a trans- or retroperitoneal approach was optional [13]. If a para-aortic lymphadenectomy was performed, it was extended to the level of the left para-aortic vein [14].

Radiotherapy and Brachytherapy

Radiotherapy was delivered to the pelvis for a total dose of 45–50 Gy, delivered in five fractions of 1.8–2 Gy per week followed, 1–2 weeks later, by intracavitary brachytherapy. Pelvic radiation was delivered using a four-field box technique (anteroposterior, posteroanterior, and two lateral fields) with x-ray energy of at least 4-MV photons. The pelvic field extended from the upper margin of L5 to the midportion of the obturator foramen or the lowest level of disease, with a 2–3-cm margin, and laterally 1.5–2 cm beyond the lateral margins of

the bony pelvic wall (at least 7 cm from the midline). For the lateral fields, the anterior border was the anterior border of the pubic symphysis and the posterior border was the space between S2 and S3. Radiation fields could be modified to include areas of known tumor. This radiation was combined with concomitant chemotherapy using cisplatin (40 mg/m² weekly) during external radiation therapy.

The brachytherapy dose was 15 Gy according to International Commission on Radiation Units recommendations [15], taking into account tumor extension at the time of diagnosis and, potentially, imaging findings at the time of brachytherapy with the vaginal mould in place in order to accurately define the target volume, taking into account the doses to critical organs (mainly the bladder and rectum). For some patients, Fletcher-Suit or Delouche systems were used at the time of brachytherapy (depending on the usual practice of each team). If two intracavitary applications were used, the second was to be given within 2 weeks after the first implant. The use of a sixth course of concomitant chemotherapy during brachytherapy was optional.

Six to 8 weeks after the end of brachytherapy, clinical and radiological responses were evaluated by both gynecological examination and MRI. Patients with clinical or radiological residual disease were treated surgically and were not considered as potential candidates for the trial. Patients having achieved a complete clinical and radiological response (and who gave their informed consent) were then randomly allocated to the treatment arms: hysterectomy (arm A) or no hysterectomy (arm B). Hysterectomy could be performed using a laparotomy or a laparoscopic approach and could be extrafascial or radical (type II according to the Piver classification [16]) according to the preoperative examination. A selective or complete pelvic lymphadenectomy was optional and could be performed if lymphadenopathy was detected during surgery. If a para-aortic lymphadenectomy was not performed initially using a laparoscopic approach, it could be done at the time of pelvic surgery in patients randomized to arm A. It was possible for some of the patients randomized to arm B to undergo surgery after brachytherapy to carry out a laparotomy or a laparoscopic para-aortic lymphadenectomy, but without pelvic surgery. Whatever the timing of this surgery, if a para-aortic lymphadenectomy was done, it was performed from the aortic bifurcation up to the level of the left renal vein.

Follow-Up

During CRT, patients were evaluated weekly by clinical examination and a blood count. After the end of the treatment, clinical examination was performed at least every 3 months during the first 2 years of this trial and then every 6 months during the next 3 years. Every 6 months for the 2 first years, then every year, a systematic (abdomino)-pelvic MRI or CT scan was performed. Chest x-ray was performed every year. Pap smears were optional.

Morbidities during and after the treatment were graded using the Franco-Italian glossary (but results of morbidities are studied in a further publication) [17].

Statistical Analysis

The main endpoint of this study was the 3-year EFS rate. The EFS duration was calculated from the date of randomization to the date of the first event (local or distant recurrence or death) or the last follow-up for patients free of recurrence. The study was designed to detect a 10%–15% higher EFS rate at 3 years in arm A with at least 80% power and a 5% level of significance: 160 patients had to be enrolled in each arm. Stratification between the two arms was according to two criteria: disease stage (IB2 or II) and pelvic nodal status based on preoperative imaging.

RESULTS

Unfortunately, this trial was closed because of poor accrual: only 61 patients were enrolled (in 2003–2006) and are reported on here: 31 in arm A and 30 in arm B. Patient characteristics per treatment group are detailed in Table 1.

Initial Characteristics

Respectively, 26 and 10 patients had clinical spread to the parametria or vagina during initial management. During pretherapeutic examinations, 18 patients had suspicious pelvic nodes (on MRI and/or CT scan). No patient had suspicious para-aortic nodes. Thirteen patients underwent an initial para-aortic lymphadenectomy (associated with pelvic node dissection in one). Two patients had involved para-aortic nodes and one patient had positive pelvic nodes (of 17 removed) but without para-aortic involvement.

Treatment Modalities

A CONSORT diagram of the trial is given in Figure 1. All patients except one received CRT and brachytherapy according to the previously defined inclusion criteria. That patient (in arm B) underwent a radical hysterectomy. One patient, included initially in arm A, refused hysterectomy and was treated exclusively with CRT and brachytherapy. Thus, one patient initially included in arm A did not undergo hysterectomy and one patient included in arm B did undergo hysterectomy. Except for those two cases, patients randomized to both arms received the planned surgical treatment.

The median number of courses of concomitant cisplatin chemotherapy was five (range, 3–7). The median total dose of cisplatin administered per patient was 343 mg (range, 190–534 mg). After the end of CRT and brachytherapy all patients, except four, had a normal clinical examination (but this status was unknown for eight patients). Those four patients had an “ambiguous” clinical lesion in the cervix (fibrosis) without any obvious sign of clinical residual disease. Twenty-eight patients underwent a Pap test before randomization. Three had abnormal results: two had hemorrhagic and/or post-therapeutic cytological aspects and one had “suspicious” Pap smears but with normal biopsies of the cervix.

During prerandomization imaging (MRI examination), six patients had “residual” cervical disease measuring 6–20 mm. The patient with disease measuring 20 mm was in arm B (no hysterectomy) and was still disease free at the time of the last

Table 1. Characteristics of patients in both arms

Characteristic	Total, <i>n</i> (%)	Arm A, hysterectomy	Arm B, no hysterectomy	<i>p</i> -value
Median (range) age, yrs	45 (24–69)	45 (24–69)	44 (28–69)	NS
Stage				
IB2	31 (51%)	16 (52%)	15 (50%)	NS
II	30 (49%)	15 (48%)	15 (50%)	
Histologic subtype				
Squamous cell	52 (85%)	28 (90%)	24 (80%)	NS
Adenocarcinoma	9 (15%)	3 (10%)	6 (20%)	
Initial surgical para-aortic staging	13 (21%)	7 (23%)	6 (20%)	NS
Para-aortic nodal involvement ^a	2	1	1	
Suspicious pelvic nodes on preoperative imaging	18 (30%)	9 (29%)	9 (30%)	NS
Median (range) <i>n</i> of fractions of ERT	25 (13–28)	25 (13–28)	25 (23–28)	NS
Unknown	7	5	2	
Median (range) dose of ERT, Gy	45 (40–57)	45 (40–57)	46 (40–57)	NS
Brachytherapy				
One application	49	24	25	NS
Two applications	6	4	2	
Unknown	6	3	3	
<i>n</i> patients receiving lateropelvic ERT boost	14 (26%)	6 (23%)	8 (31%)	NS
Unknown	19	11	8	
Median (range) dose of brachytherapy, Gy	15 (10–35)	15 (15–22)	15 (10–35)	NS
Unknown	9	7	2	
Median (range) duration of RT, ^b days	51 (35–134)	51 (36–80)	51.5 (35–134)	NS
Unknown	5	1	4	
<i>n</i> courses of concurrent chemotherapy	5 (3–7)	5 (3–7)	5 (4–7)	NS
Unknown	5	1	4	
Total (range) dose of cisplatin administered, mg	343 (190–534)	342 (190–420)	350 (200–534)	NS
Unknown	10	3	7	
Positive pelvic nodes at completion surgery	4 (12%)	3 (15%)	1 (8%)	NS
Unknown	11	11	0	
Positive para-aortic nodes at completion surgery	2 (5.5%)	2 (10%)	0	NS
Unknown	9	9	0	

^aPara-aortic involvement after initial surgical staging.^bMedian duration from the first day of ERT until the last day of brachytherapy or boost of ERT if done.

Abbreviations: ERT, external radiation therapy; NS, not significant; RT, radiation therapy.

follow-up. In the last case with an “abnormal” MRI examination, the type of abnormality was unknown.

Twenty-nine patients underwent biopsies of the cervix before randomization to rule out histological residual disease (particularly patients with abnormal clinical or radiologic exams): 25 had normal biopsies and one had fibrotic tissue according to the histological analysis.

In arm A, a laparoscopic hysterectomy was performed in seven cases and a radical hysterectomy was performed in 10 cases. Sixteen patients underwent para-aortic lymphadenectomy. Six patients underwent complete bilateral pelvic lymphadenectomy, three had a unilateral pelvic lymphadenectomy with con-

tralateral pelvic selective adenectomy, and four had a selective pelvic adenectomy. In arm B, 17 patients underwent a para-aortic lymphadenectomy (via a laparoscopic approach for six of them). No patient underwent a complete pelvic lymphadenectomy and one patient had a selective pelvic adenectomy.

In arm A, 11 patients had residual disease after histological analysis (isolated cells for six patients, ≤ 1 cm for three patients, and > 1 cm for two patients). Only one of them (with residual disease > 1 cm) had an abnormal prerandomization MRI (ambiguous endocervical lesion measuring 8 mm). In arm A, three patients had metastatic pelvic nodes (two had one involved node and one had three involved nodes) and two pa-

Figure 1. CONSORT 2010 flow diagram of the GYNECO 02 trial.

tients had metastatic para-aortic nodes (one had two involved nodes and one had eight involved nodes). In arm B, one patient had metastatic pelvic nodes and no patient had metastatic para-aortic nodes.

Recurrence and Survival

The median duration of follow-up was 3.8 years (range, 0.4–5.8 years). Twelve patients relapsed (five of them died): eight in arm A and four in arm B. The location of recurrent disease was known in 11 patients (Table 2). Among two patients having a pelvic node recurrence, none had a suspicious pelvic node during initial imaging and one had lateropelvic boost for parametrial spread. The 3-year EFS rates were, respectively, 72% (95% confidence interval [CI], 53%–85%) and 89% (95% CI, 75%–96%) (not significant [NS]) in arm A and arm B. The 3-year OS rates were, respectively, 86% (95% CI, 69%–95%) and 97% (95% CI, 83%–99%) (NS) in arm A and arm B. The log-rank test did not show any statistical difference between arm A and arm B in terms of the OS and EFS outcomes (Figs. 2 and 3).

DISCUSSION

The Gynecologic Oncology Group 71–Radiation Therapy Oncology Group 84–22 trial was performed nearly 20 years ago during the era of external-beam radiation, and it investigated the therapeutic value of extrafascial hysterectomy after external-beam radiation therapy for locally advanced cervical cancer [18]. That trial exclusively included patients with stage IB2 cervical cancer treated using external radiation therapy (with

Table 2. Site of first recurrence according to randomization arm

Location of the first recurrence	Arm A, hysterectomy (n = 31)	Arm B, no hysterectomy (n = 30)
Centropelvic alone (n = 3)	1	2
Centropelvic and nodal (n = 1)	1	–
Pelvic node and distant (n = 1)	1	–
Para-aortic nodes alone (n = 1)	1	–
Para-aortic nodes and distant (n = 3)	3	–
Distant without pelvic or nodal involvement (n = 2)	1	1
Total	8	3

cobalt or higher energy accelerators) and intracavitary brachytherapy. Patients were thereafter randomized between extrafascial and no hysterectomy. Two-hundred fifty-six patients were eligible (132 in the hysterectomy arm and 124 in the exclusive radiation therapy arm). There was no difference in

Figure 2. Kaplan–Meier estimates of the overall survival rate for patients in arm A (hysterectomy) and arm B (no hysterectomy).

Figure 3. Kaplan–Meier estimates of the event-free survival rate for patients in arm A (hysterectomy) and arm B (no hysterectomy).

terms of survival between the two arms (hysterectomy versus no hysterectomy), but the 5-year local relapse rates were 27% in the external radiation alone arm and 14% in the external radiation therapy followed by extrafascial hysterectomy arm [18]. Other retrospective studies suggested that surgery after external radiation therapy could exert a potential therapeutic impact [3–10], but none of those studies were randomized trials. After 1999, the use of CRT became the new standard for the treatment of cervical cancer >4 cm [1, 2]. Several countries (mainly in Europe and Asia) considered CRT as neoadjuvant therapy and proposed hysterectomy in this context [3–10]. Nevertheless, this surgery could impair the postoperative quality of life of patients because there is a potential risk for major morbidities with CRT, which should be clearly balanced with the true therapeutic benefit of such a hysterectomy [19].

This is why only a randomized trial could adequately determine whether or not completion surgery would be therapeutically beneficial. Such a trial was opened in France 6 years ago. Only patients with a macroscopic and radiological complete response after CRT for stage IB2 or II cervical cancer were included because most of the teams participating in the trial considered that the presence of residual disease at the end of CRT and brachytherapy might be an indication for surgery

after CRT [6, 10, 20]. Nevertheless, the true therapeutic impact of surgery in such cases is really unproven because patients with macroscopic residual disease after CRT have a higher risk for extracervical disease (nodal spread or extrapelvic spread) that cannot be adequately cured using surgery [6, 19]. In order to improve the rate of participation and inclusion of patients from about 25 centers that agreed to include patients in this trial, we selected the patient population for whom the balance between morbidity and the therapeutic impact of surgery was highly uncertain, namely, patients with a complete macroscopic and radiological response at the end of treatment (i.e., the majority of patients with stage IB2 and II cervical cancer after CRT). Even though inclusion criteria were unanimously validated by all the colleagues who agreed to participate in our trial, the trial had to be closed after 3 years because of a lack of recruitment. How can we explain such a “failure”? The first explanation is that, in a country where most physicians (general physicians or gynecologists) who give advice to patients consider that the “initial site” of tumor (uterine cervix) should be surgically removed after CRT, some patients also insist on having a hysterectomy after treatment. This is the first explanation (but not the overriding one). Probably the most important explanation is that it was very difficult to truly convince colleagues who participated in this trial (and who are really well versed in the natural history and treatment of cervical cancer) to actually include patients and thus to agree to question their personal convictions (the majority of them were in favor of completion surgery).

Even though this trial was closed because of insufficient accrual, 61 patients were included and were investigated. Although the study was underpowered because of its limited size, it is important because some interesting results were observed. The first important finding is that nearly one third of the patients undergoing adjuvant hysterectomy (10 of 31) with a complete clinical and radiological response still had residual disease on histological analysis of the hysterectomy specimen. Six of them had residual disease limited to a few active isolated cells, and the prognosis for those patients is probably very close to that of patients with a histological complete response [4, 5, 19]. Five patients had residual disease with active tumor measuring <1 cm (three patients) or >1 cm (two patients). This means that clinical and MRI examination are not fully accurate for the evaluation of response after CRT [21]. Perhaps the use of another technique (PET imaging) could help to improve the evaluation of response after treatment. However, the false-negative evaluation of complete response was evenly divided between the two arms and had no impact on the results. As we previously observed, we were unable to prove that hysterectomy improves the survival of patients with residual disease on histological analysis.

The second finding in this population of patients without macroscopic residual disease at the end of CRT was that local failure was rare. Of 61 patients, only four developed a centropelvic (pure or mixed) recurrence. This low rate demonstrates that the combination of CRT and brachytherapy yields excellent local control. Surely, this result could be explained by the fact that patients with a higher risk for local failure are those

exhibiting macroscopic residual disease at the end of treatment and those patients were excluded from this trial. Nevertheless, the proportion of such cases is small in the overall population of patients with stage IB2 and II cervical cancer treated using CRT and brachytherapy. Furthermore, the use of three-dimensional brachytherapy seems to provide better local control and survival outcomes in patients after CRT in this context [22, 23]. In the present series, most of the recurrences were in fact a result of nodal (particularly para-aortic nodes) failure [24]. Such results would probably be different if this trial had been performed during the last 3 years because many of the colleagues who participated in this trial now use PET-CT imaging and some of the teams (like ours) use laparoscopic para-aortic node staging before beginning CRT. Those techniques improve the detection rate of para-aortic (or extra-abdominal) spread missed during conventional imaging and therefore seem to improve the survival outcome of patients [13, 25–28]. During the period of this trial, those procedures were not routinely used by the majority of the teams (only 13 patients underwent para-aortic node staging).

If we consider the surgery technical aspects, the morbidity rate was correlated with the radicality of the hysterectomy [19]. Patients treated using radical hysterectomy and parametrial dissection had a higher rate of postoperative morbidity (particularly urinary tract and bowel morbidities). Such radical hysterectomy could be discussed in cases of bulky residual disease, but it is probably not necessary (except if required for technical reasons) if patients have achieved a complete re-

sponse. In such cases, an extrafascial hysterectomy is sufficient. The use of a laparoscopic approach could also reduce the morbidity rate in this context [8]. However, lowering the morbidity rate does not justify the indication for this surgery from an oncological point of view. Finally, despite the lack of power for this study, the most important result of this trial is that hysterectomy does not appear to have an impact on survival outcomes. OS and EFS rates were similar in both arms. Since the closure of this trial, surgery still remains optional (or not performed) for patients with a complete clinical and radiological response after CRT (evaluated 8–10 weeks after brachytherapy) in several institutions that participated in this trial.

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