Clinical Investigation

Chemoradiation With Concomitant Boosts Followed by Radical Surgery in Locally Advanced Cervical Cancer: Long-term Results of the ROMA-2 Prospective Phase 2 Study

Gabriella Ferrandina, MD,* Antonietta Gambacorta, MD,† Valerio Gallotta, MD,* Daniela Smaniotto, MD,† Anna Fagotti, MD,† Luca Tagliaferri, MD,† Elvira Foti, MD,* Francesco Fanfani, MD,* Rosa Autorino, MD,† Giovanni Scambia, MD,* and Vincenzo Valentini, MD

*Division of Gynecologic Oncology, Catholic University of the Sacred Heart, Rome, Italy; †Division of Radiotherapy, Catholic University of the Sacred Heart, Rome, Italy; and ‡Gynecologic Surgery, University of Perugia, Terni, Italy

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**Summary**

Addition of concomitant boosts to the accelerated fractionation modality to whole-pelvis chemoradiation followed by radical surgery resulted in a high rate of pathologically assessed complete response to chemoradiation therapy. The 3-year local failure rate was 7%, and the 3-year disease-free survival and overall survival rates were 73.0% and 86.1%, respectively. These results appear very encouraging considering the

**Purpose:** This prospective, phase 2 study aimed at assessing the efficacy of accelerated fractionation radiation therapy by concomitant boosts (CBs) associated with chemoradiation therapy (CRT) of the whole pelvis, in improving the rate of pathological complete response (pCR) to treatment in patients with International Federation of Gynaecology and Obstetrics (FIGO) stage IB2-IVA locally advanced cervical cancer.

**Methods and Materials:** Neoadjuvant CRT included conformal irradiation of the whole pelvis with a total dose of 39.6 Gy (1.8 cGy/fraction, 22 fractions), plus additional irradiation of primary tumor and parametria with 10.8 Gy administered with CBs (0.9 cGy/fraction, 12 fractions, every other day). Concomitant chemotherapy included cisplatin (20 mg/m², days 1-4 and 26-30 of treatment), and capecitabine (1300 mg/m²/daily, orally) during the first 2 and the last 2 weeks of treatment. Radical hysterectomy plus pelvic with or without aortic lymphadenectomy was performed within 6 to 8 weeks from CRT. Toxicity was recorded according to Radiation Therapy Oncology Group toxicity criteria and Chassagne grading system. Based on the Simon design, 103 cases were required, and the regimen would be considered active if >45 pCR were registered (α error = 0.05; β error = 0.1).

**Results:** pCR was documented in 51 cases (50.5%), and the regimen was considered active, according to the planned statistical assumptions. At median follow-up of 36 months (range: 7-85 months), the 3-year local failure rate was 7%, whereas the
3-year disease-free and overall survival rates were 73.0% and 86.1%, respectively. Grade 3 leukopenia and neutropenia were reported in only 1 and 2 cases, respectively. Gastrointestinal toxicity was always grade 1 or 2.

Conclusions: Addition of CBs in the accelerated fractionation modality to the whole pelvis chemoradiation followed by radical surgery results in a high rate of pathologically assessed complete response to CRT and a very encouraging local control rate, with acceptable toxicity. © 2014 Elsevier Inc.

Introduction

Even with the advent of exclusive chemoradiation therapy (CRT), which has represented the standard treatment for locally advanced cervical cancer (LACC) since 1999 (1, 2), 5-year overall survival (OS) in this subset of patients remains around 70%; in this context, investigational approaches using either neoadjuvant chemotherapy (NACT) or CRT followed by radical surgery (RS) have reported encouraging results in terms of clinical outcome (3-6).

Recently published phase 3 randomized studies demonstrated that CRT followed by RS is not superior to exclusive CRT but results are feasible and safe (7, 8); indeed, the rate of early complications was in the range reported after NACT plus RS, as well as after exclusive CRT (3-6, 8-10), whereas long-term toxic effects (proctitis, cystitis, hydronephrosis) results were even lower than with exclusive CRT (8, 11-13) because of replacement of uterovaginal brachytherapy with completion surgery (5, 6, 11). Surgery also represents the only method to reliably obtain the most important prognostic information, that is, pathological response to treatment (5, 6, 8), as imaging techniques have been shown not to be able to accurately detect residual tumor after neoadjuvant approaches (14). Pathological assessment of response to treatment might have clinically relevant implications for definition of risk and pattern of recurrence, individualized patient counseling, and choice to administer adjuvant treatment.

Based on the close relationship between pathological response to neoadjuvant therapies and outcome (5, 6), several efforts have been made in the last decade to modify dose and fractionation of cisplatin-based CRT, treatment time length or irradiated volumes (15-17), in order to increase sensitivity to treatment and improve local control. In this context, the feasibility of accelerated fractionation radiation therapy by concomitant boosts (CB) associated with cisplatin-based chemotherapy has been investigated in the ROMA-1 phase 1 study: the dose of 39.6 Gy (1.8 cGy/fraction, 22 fractions) to the whole pelvis and the total dose of 50.4 Gy (39.6 Gy plus 10.8 Gy administered with concomitant boosts, 0.9 cGy/fraction, 12 fractions) to primary tumor and parametria were established as the recommended dosages for further studies (15).

Here we report the final, long-term results of the ROMA-2 phase 2 study, aimed at assessing the efficacy of this regimen in improving rates of pathologically assessed complete response to treatment and clinical outcome. Details of acute and late toxicity are also presented.

Methods and Materials

Study design and endpoints

This was a prospective, phase 2 study aimed at evaluating the efficacy of preoperative CRT with concomitant boosts in LACC patients. The primary endpoint was represented by rate of pathologically assessed complete response to treatment, and secondary endpoints were disease-free survival (DFS), OS, and acute as well as late toxicity.

Eligibility

Patients with Fédération Internationale de Gynécologie et d’Obstétrique (FIGO [International Federation of Gynecology and Obstetrics]) stage IB2-IVA LACC disease were evaluated for enrollment in the study by the tumor board which included gynecologic oncologists and radiation therapists. The trial was approved by the local Ethics Committee and Institutional Review Board (P/258/CE/2006), and all patients signed a written informed consent agreeing to submit to all the procedures described and for their data to be collected.

Inclusion criteria were biopsy-proven carcinoma of the cervix (stage IB2-IVA), no evidence of distant disease, age ≤80 years old, Eastern Cooperative Oncology Group performance status ≤2, adequate bone marrow function (white blood cell count >3000 cells/mm³; platelets >120,000 cells/mm³), adequate renal function (blood urea nitrogen <25 mg/dL; creatinine <1.5 mg/dL), normal liver function (bilirubin <2 mg/dL), no previous cancer other than basal cell carcinoma.

Exclusion criteria were previous or concurrent malignancies at other sites with the exception of basal or squamous cell carcinoma of the skin and uncontrolled severe infection and/or medical problems unrelated to malignancy which would limit full compliance with the study or expose the patient to extreme risk.

Pretreatment workup included collection of medical history, clinical examination, chest radiography, abdominopelvic magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT).
scan in order to exclude cases with distant sites of disease; complete blood count, and measurement of liver and renal function, as well as cystoscopy and proctoscopy in case of clinical suspicion of bladder and/or rectum invasion.

**Chemoradiation therapy and technique details**

Neoadjuvant CRT included conformal irradiation of the pelvic lymph node drainage, bulky tumor, and parametria with a total dose of 39.6 Gy (1.8 cGy/fraction, 22 fractions), plus additional irradiation of primary tumor and parametria with 10.8 Gy administered with CBs (0.9 cGy/fraction, 12 fractions every other day) (16). Concomitant chemotherapy included cisplatin (20 mg/m², 2-h intravenous infusion, on days 1-4 and 26-30 of treatment) and capecitabine (1300 mg/m²/daily, orally) during the first 2 and last 2 weeks of treatment.

Radiation therapy was delivered with a 4-field box technique to the pelvic region. All patients were treated in the prone position on an up-down table device (18). Twenty-two fractions were delivered over 5 days/week, using photon energies of 10 MV. The clinical target volume 2 (CTV2), including primary tumor, internal iliac obturators, external iliac lymph nodes, and the upper third of vagina, received a dose of 39.6 Gy. In patients with stage IIIA disease, inguinal lymph nodes were included in the irradiation field. CBs were delivered to primary tumor mass and parametria (CTV1, determined by comparison between the simulation CT scan and the staging MRI through 4 coplanar, 2-by-2 opposite, oblique fields during whole-pelvis irradiation).

**Clinical response assessment and surgery**

Objective response to treatment was evaluated according to Response Evaluation Criteria for Solid Tumors (RECIST) criteria (19) 4 to 6 weeks after completion of CRT; patients achieving response to treatment underwent triage for radical hysterectomy according to Piver et al. (20), and pelvic, with or without aortic, lymphadenectomy within 6 to 8 weeks from completion of CRT. Aortic lymphadenectomy was performed in case of (1) positive pelvic lymph nodes on frozen section analysis, routinely performed during completion surgery; (2) positive pelvic lymph nodes on imaging at initial staging work up; and (3) intraoperatively assessed suspicious aortic lymph nodes.

Pathologic response to therapy was evaluated based on the examination of uterus, vaginal cuff, parametrium, and pelvic and aortic lymph nodes: residual disease at any site was expressed in millimeters, and response was defined as complete (absence of any residual tumor after treatment at any site level), microscopic (persistent tumor foci ≤3 mm maximum dimension), or macroscopic (persistent tumor foci >3 mm maximum dimension). Adjuvant treatment with a platinum-taxane combination was administered in case of pathologic involvement of vaginal margins and/or lymph nodes, and/or presence of lymph-vascular space invasion.

**Toxicity assessment**

Toxicity assessment was performed according to Radiation Therapy Oncology Group toxicity criteria and Chassagne grading system (21, 22). Acute toxicity was assessed weekly during treatment. After surgery, patients underwent physical examination, complete blood count, and blood chemistry every 3 months for the first 2 years and every 6 months thereafter. Chest radiography and abdominopelvic MRI were performed every 6 months for the first 3 years and every 12 months thereafter.

**Statistical analysis**

Sample size was quantified based on previous studies reporting a rate of pathologically assessed complete response to treatment around 40% on average (5-7, 16,23-25).

Using the mini-max 2-stage design by Simon (26), we tested the null hypothesis that the true rate of pathologically assessed complete response to treatment would improve from 40.0% to the clinically relevant alternative of 55.0% by using an α error of 0.05 and a β error of 0.1. Thus, the first step was planned to include 62 patients; if >24 patients successfully achieved pathological complete response to CRT, the study would enroll an additional 32 patients, up to a total of 94 patients. The regimen would be considered active if >45 pathological complete responses were registered. Considering a dropout rate of approximately 10%, 103 cases were planned to be enrolled.

The χ² test or Fisher exact test for proportion was used to analyze the distribution of clinicopathological variables according to different subgroups. The Wilcoxon rank sum nonparametric test was used to analyze the distribution of continuous values. The 95% confidence intervals (CI) were calculated by using the Wald method (27).

Locoregional failure was defined as any failure in the pelvis. DFS was calculated from the date of surgery to the date of relapse or date of the last follow-up; OS was calculated from the date of diagnosis to the date of death or date of the last follow-up. Median values and life tables were computed using the product limit estimate by Kaplan-Meier method (28), and the log-rank test was used to assess statistical significance (29). Statistical analysis was carried out using Solo software (BMDP Statistical Software, Los Angeles, CA).

**Results**

Figure 1 shows the Consolidated standards for reporting trials (CONSORT) diagram relative to our study population: between January 2007 and May 2012, 105 patients
were screened, and 103 were enrolled in the study due to the occurrence of screening failure in cases. Clinical and pathological characteristics of enrolled patients are summarized in Table 1; median age was 52 years old (range: 22-74 years of age). Seventy-eight patients (75.7%) were FIGO stage IIB, whereas 15 cases (14.6%) had stage III disease. At staging workup, pelvic lymph node involvement was documented in 47 patients (45.6%).

Clinical complete and partial response to treatment were documented in 36 (34.9%) and 63 (61.2%) patients, respectively. Because 2 patients experienced progression of disease during CRT, radical surgery was performed in 101 patients (98.0%).

Median time interval from completion of CRT to radical surgery was 7 weeks (range: 6-10 weeks), and only 15 patients (15.1%) underwent surgery after the planned time interval due to logistic reasons (n=12) and a more prolonged time required to recover from CRT toxicity (n=3).

Sixteen patients (15.8%) underwent type II radical hysterectomy, whereas 82 cases (81.2%) underwent type III radical hysterectomy; pelvic lymphadenectomy was performed in all cases, whereas aortic lymphadenectomy was performed in 18.8% of cases. As shown in Table 2, pathologic complete response to treatment was documented in 51 cases (50.5%), whereas 32 cases (31.7%) showed microscopic response.

There were no statistically significant differences in the distribution of pathological response to treatment according to stage of disease; in particular, the rates of pathological complete, microscopic, and macroscopic responses were 51.1%, 29.5%, and 19.3%, respectively, in stage IB-IIIA patients compared to 46.1%, 69.2%, and 7.7%, respectively, in stage IIIB-IVA patients (data not shown). Pathologic involvement of pelvic and aortic lymph nodes was reported in 11 of 101 patients (10.9%) and in 3 of 19 cases (15.8%), respectively (data not shown).

We did not document any case of pathologically involved tissue margins. Twelve patients (11.9%) required adjuvant chemotherapy (data not shown).

Toxicity

Toxicity was evaluated in all patients: as far as hematological toxicity was concerned, leukopenia was the toxicity

![Fig. 1. CONSORT flow diagram of the study population.](image-url)
most frequently reported (39.8%), whereas anemia was documented in 12.6% of cases; and grade 3 leukopenia and neutropenia were reported in only 1 and 2 cases, respectively (Table 3).

Gastrointestinal toxicity was the nonhematological toxicity most frequently documented but was always grade 1 or 2. Genitourinary side effects were grade 1 in 11.6% of patients and grade 2 in 2.9% of cases. Skin toxicity was registered in only 6 patients and was mild in most of them. All patients completed the full cycles of chemotherapy and radiation therapy. Temporary interruption of CRT for >4 days was required in 4 patients (3.9%).

### Complications

Intraoperative complications were registered in 2 patients (bladder and ureter injury) which were successfully managed during surgery (data not shown). During the observation period, 12 of 101 of patients (11.9%) experienced early postoperative complications, but only 2 had grade 3 toxicity. As shown in Table 4, there were 18 early complications, and most of them were vascular (n=9) and urinary (n=7). Five patients had late postoperative complications, and only 1 experienced grade 3 toxicity. The total number of late postoperative complications was 7, of which 4 were ≥grade 2.

### Clinical outcome

As of March 2014, median duration of follow-up in the whole series was 36 months (range: 7-85 months). Overall, 98 patients (95.1%) were followed for at least 2 years, whereas 64 patients were followed for at least 3 years.

Recurrence and/or progression of disease was documented in 25 cases (24.3%): in particular, 4 patients (3.9%) developed isolated pelvic lymph node recurrence, and 4 patients has isolated aortic lymph node recurrence, whereas isolated liver, spleen, and lung recurrences were documented in 6 patients (5.8%); only 1 patient experienced peritoneal carcinomatosis, and 10 cases (9.7%) developed mixed sites of disease relapse. There was no case of central pelvic relapse of disease. Death of disease was documented in 13 patients (12.9%).

The 3-year locoregional failure was 7% (data not shown). As shown in Figure 2 A and B, 3-year DFS and OS rates in the whole series were 73.0% and 86.1%, respectively. Patients achieving pathological complete response to treatment experienced a statistically significant better DFS rate than those with microscopic (P = .048) or macroscopic

### Table 3 Acute toxicity per patient (N=103)

<table>
<thead>
<tr>
<th>Toxicity type</th>
<th>No. of patients with toxicity grade shown (%)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological</td>
<td>Anemia</td>
<td>12 (11.6)</td>
<td>1 (1.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Leukopenia</td>
<td>20 (19.4)</td>
<td>20 (19.4)</td>
<td>1 (1.0)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td>1 (1.0)</td>
<td>2 (1.9)</td>
<td>2 (1.9)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>4 (3.9)</td>
<td>4 (3.9)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nonhematological</td>
<td>Gastrointestinal</td>
<td>33 (32.0)</td>
<td>10 (9.7)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Genitourinary</td>
<td>12 (11.6)</td>
<td>3 (2.9)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Skin toxicity</td>
<td>5 (4.8)</td>
<td>1 (1.0)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Table 4 Type of early and late postoperative complications according to organ system and grade

<table>
<thead>
<tr>
<th>Organ system</th>
<th>No.</th>
<th>Early</th>
<th>Type</th>
<th>Late</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>25</td>
<td>18</td>
<td>-</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Urinary</td>
<td>10</td>
<td>7</td>
<td>-</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>1</td>
<td>1</td>
<td>Mild, occasional hematuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>6</td>
<td>4</td>
<td>Ureteral stenosis requiring surgery with subsequent normal function (n=3)</td>
<td>2</td>
<td>Ureteral stenosis requiring surgery with subsequent normal function (n=1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vesicovaginal fistula with complete healing and normal function after treatment (n=1)</td>
<td></td>
<td>Urinary retention &lt;6 months (n=1)</td>
</tr>
<tr>
<td>G3</td>
<td>3</td>
<td>2</td>
<td>Vesicovaginal fistula with permanent anatomic and/or functional damage (n=2)</td>
<td>1</td>
<td>Ureteral stenosis requiring surgery with subsequent inadequate function (n=1)</td>
</tr>
<tr>
<td>Vascular</td>
<td>12</td>
<td>9</td>
<td>-</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>11</td>
<td>9</td>
<td>Lymphocele not requiring drainage (n=8)</td>
<td>2</td>
<td>Lymphocele not requiring drainage (n=1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Thrombophlebitis on medical treatment (n=1)</td>
<td></td>
<td>Thrombophlebitis on medical treatment (n=1)</td>
</tr>
<tr>
<td>G2</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>Lymphocele requiring drainage (n=1)</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>2</td>
<td>Abdominal wound dehiscence not requiring surgery (n=1)</td>
<td>1</td>
<td>Abdominal wound dehiscence not requiring surgery (n=1)</td>
</tr>
<tr>
<td>G1</td>
<td>2</td>
<td>1</td>
<td>Pelvic abscess requiring surgical drainage (n=1)</td>
<td>1</td>
<td>Abdominal wound dehiscence not requiring surgery (n=1)</td>
</tr>
<tr>
<td>G2</td>
<td>1</td>
<td>1</td>
<td>Pelvic abscess requiring surgical drainage (n=1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviation:** G = grade.
response (Fig. 2C). Similarly, pathologically complete responders achieved longer OS than patients with microscopic \((P=0.039)\) or macroscopic \((P=0.004)\) response to CRT (Fig. 2D).

**Discussion**

This phase 2 study reports the long-term results about efficacy and safety of preoperative chemoradiation with concomitant boosts in LACC patients. The administration of concomitant boosts in an accelerated fractionation modality has allowed us to deliver a higher radiation dose at the site of macroscopic disease without prolonging treatment duration, which could increase the risk of tumor cell repopulation. Indeed, the current regimen provided a very high rate of clinical response (96%) and operability (approximately 98%); moreover, as far as the primary endpoint is concerned, we reported a rate of pathological complete response to CRT of 50.5%. This figure, which derives from a robust statistical analysis due to the large number of patients enrolled and the power of the study, must be considered clinically relevant compared to the average of rates of pathological complete response to CRT reported in previous experiences \((16,17,23-25)\). One could argue that the advantages related to the acquisition of data about pathologically assessed response to treatment could not be adequately justified by the potentially higher risk of complications due to the use of surgery after CRT; indeed, this represents a situation harboring radiation-induced tissue sequelae, such as inflammation, vascular fibrosis, firm adhesions, and others, which are expected to increase postoperative morbidity. In this context, our current findings appear more favorable than those of other experiences using CRT followed by RS, as we documented only 3% of patients experiencing grade 2 postoperative complications, although we adopted radical hysterectomy instead of extrafascial hysterectomy \((5,6,23,24)\). In addition, a recently published phase 3 trial comparing efficacy and safety of CRT followed by RS versus efficacy and safety of CRT plus brachytherapy reported rates of early complications between the 2 treatment arms that were equivalent, whereas late morbidity (proctitis, cystitis, hydronephrosis) results were even lower in CRT followed by RS than in exclusive CRT, probably because of replacement of uterovaginal brachytherapy with completion surgery \((5,6,11)\).
We reported extrapelvic recurrence with or without pelvic disease, in approximately 18% of cases; although this rate is in the range registered in studies using different multimodal therapeutic approaches to LACC patients (2, 12, 31, 32), this finding unexpectedly raises the question whether the strenuous pursuit of increased local control would necessarily translate into prevention of distant relapse and prolongation of survival. Otherwise, additional efforts aimed at eradicating micrometastatic disease through the addition of systemic, not radiation-sensitizing, treatment should be attempted. Indeed, some evidence from meta-analyses of individual patient data from randomized trials and other preliminary studies have suggested the potential efficacy of chemotheraphy when added to CRT as adjuvant treatment (2, 32, 33). Moreover, NACT has been reported to result in a high rate of response to CRT (34) and to provide longer DFS and OS than CRT only in a phase 3 randomized study of stage IIB-IVA patients (35). While awaiting the full exploitation of the therapeutic potential of growth and proangiogenic growth factor inhibition (36, 37), it must be acknowledged that the ongoing INTERLACE phase 3 randomized study (NCT01566240; www.nih/clinicaltrials.gov) is testing the efficacy of carboplatin/paclitaxel containing NACT followed by CRT compared to the current standard.

Conclusions

In conclusion, we showed that the addition of concomitant boosts in accelerated fractionation modality to whole-pelvis chemoradiation therapy followed by RS results in a high rate of pathologically assessed complete response to CRT and a very encouraging local control rate, with an acceptable rate and profile of toxicity. In order to improve the outcome of patients faced with a high risk of extrapelvic relapse, we recently launched a phase 2 study using carboplatin/paclitaxel containing NACT before administering the current approach.

References


