



Multimodality approach in extra cervical locally advanced cervical cancer: chemoradiation, surgery and intraoperative radiation therapy. a phase II trial

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Authors: G. Giorda, M.D. G. Boz, M.D. A. Gadducci, M.D. E. Lucia, M.D. G. De Piero, M.D. A. De Paoli, M.D. R. Innocente, M.D. M. Trovò, M.D. R. Sorio, M.D. E. Campagnutta, M.D.

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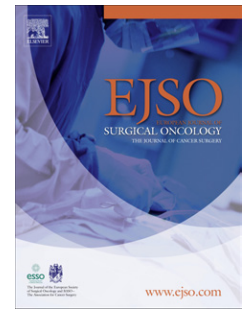
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MULTIMODALITY APPROACH IN EXTRA CERVICAL LOCALLY ADVANCED CERVICAL
CANCER: CHEMORADIATION, SURGERY AND INTRAOPERATIVE RADIATION
THERAPY. A PHASE II TRIAL

G. Giorda M.D.^a, ggiorda@cro.it

G. Boz M.D.^b, gboz@cro.it

A. Gadducci M.D.^c, a.gadducci@obgyn.med.unipi.it

E. Lucia M.D.^a, elucia@cro.it

G. De Piero M.D.^a, gdepiero@cro.it

A. De Paoli M.D.^b, adepaoli@cro.it

R. Innocente M.D.^b, rinnocente@cro.it

M. Trovò M.D.^b, mtrovo@cro.it

R. Sorio M.D.^d, rsorio@cro.it

E. Campagnutta M.D.^a ecampagnutta@cro.it

from the Centro di Riferimento Oncologico (C.R.O) - I.R.C.S.S..

National Cancer Institute (a)Gynecologic Oncology Unit, (b) Radiotherapy Unit, (d) Clinical
Oncology Unit, Via Franco Gallini 2, 33081 Aviano (PN), Italy and from (c) University of
Pisa Gynecologic and Obstetrics Clinic

Corresponding Author: Giorgio Giorda MD;

CRO via Franco Gallini 2, 33081 Aviano (PN) Italy;

Phone: +39-0434-657037 Fax: +39-0434-657049

e-mail: ggiorda@cro.it

ABSTRACT

BACKGROUND. The goal of this study was to determine the rational of radical surgery with intraoperative high-dose radiotherapy after chemoradiation (RT-CT) in extra cervical locally advanced cervical cancer (LACC) patients.

METHODS. Between 2000 and 2007, 42 LACC (stage IIA bulky-IVA) patients were treated at the Gynecologic Oncology Unit of the C.R.O. of Aviano in a Phase II Clinical Trial. Radiotherapy was administered to the whole pelvic region (50.4 Gy in 28 fractions) in combination with cisplatin (60 mg/mq) plus 5FU (750 mg/mq for 4 days) on first and fifth week of RT. Radical surgery with Intra-Operative Radiation Therapy (IORT) was performed 6-8 weeks after the end of RT-CT treatment.

RESULTS. After RT-CT, 35/42 patients (83%) underwent radical surgery and IORT treatment. At pathologic examination 8/35 (23%) patients showed complete response, while the rest (27/35) had residual disease either microscopic (17/27) or gross (10/27). The 5-year disease free survival (DFS) and the 5-year overall survival (OS) were 46% and 49% respectively. There were significant better DFS and OS when residual tumor was absent or limited to the cervix, respectively 78% versus 16% and 81% versus 20% ($p < 0.001$). All recurrences occurred within 24 months from treatment.

CONCLUSIONS. RT-CT followed by surgery and IORT in LACC patients seems to be active in a subgroup of patients with pathological complete response to treatment or partial response with residual tumor limited to the cervix.

KEYWORDS: Uterine Cervical neoplasms; Locally Advanced; Chemotherapy; Sugery; Intra-operative Radiotherapy; Combined Modality Therapy

ABBREVIATIONS: Intra-Operative Radiation Therapy (IORT); in-field recurrence(IFR); out-field recurrence (OFR)

INTRODUCTION

Cervical cancer is the second most frequent cancer for mortality worldwide, due to late diagnosis in developing countries, and the associated mortality [1] correlates with the stage of the disease [2]. Nowadays, concomitant Radiotherapy and Cisplatin based chemotherapy is the standard treatment for locally advanced cases of cervical cancer (LACC, stage IB2-IVA) [3-5] .

Indeed, a meta-analysis of 13 randomised trials confirmed that concurrent chemoradiation significantly improved disease-free survival, locoregional recurrence-free survival, metastasis-free survival and overall survival compared with irradiation alone [6,7]. Also, there was a suggestion of a difference in the survival benefit with tumour stage, but not across other patient subgroups. Furthermore, neoadjuvant chemotherapy followed by radical hysterectomy contributed to satisfactory results in LACC [8-14] and a meta-analysis of 5 randomised trials showed that this treatment modality was superior to irradiation alone presenting a gain in the 5-year overall survival of 14% [11] [15]. Finally, in an Italian randomised trial, chemo-surgical treatment achieved better progression-free and overall survival compared with irradiation alone in patients with stage Ib2-IIb disease, whereas there was no significant difference in the clinical outcome between these two treatment modalities in patients with stage III_disease [12]. Actually, one of the main objectives of current research in LACC is to improve the response rate either by modifying the treatment schedule of chemoradiation or by using neoadjuvant chemoradiation followed by surgery [16-19].

To this aim, a multimodality treatment approach on women with extra cervical LACC (stage IIA bulky-IVA) was tested in a Phase II trial including neoadjuvant chemoradiation followed by radical surgery and Intra-Operative Radiation Therapy (IORT) in this clinical setting.

PATIENTS AND METHODS

Study

From January 2000 to January 2007, 42 extra cervical LACC patients with biopsy-proven carcinoma of the cervix entered a Phase II Clinical Trial on the role of surgery and IORT after concomitant chemoradiation. Inclusion criteria were: stage IIA-Bulky (>4 cm) to stage IVA disease, no evidence of disease outside the pelvis; age <75years; Eastern Cooperative Oncology Group performance status <2; adequate bone-marrow function (WBC >3000/mm³, platelets >150,000/mm³); normal liver function (blood bilirubin <2mg/dl); adequate renal function (blood urea nitrogen <25 mg/dl) and no prior cancer. All patients signed a written informed consent to participate to the experimental protocol approved by Local Research Ethics Committee.

Before accrual, the patients underwent history and clinical examination, gynecological examination, complete blood count, biochemical workup abdomino-pelvic CT scan (to exclude extra pelvic disease) and pelvic MRI (to measure the volume of pelvic neoplasia). Cystoscopy and sigmoidoscopy were performed in the case of clinical suspicion of bladder or rectal involvement.

Treatment Schedule

Treatment started with external beam radiotherapy, 4-field technique, 50.4 Gy in 28 fractions (on the pelvic field up to common iliac nodes included) and concurrent chemotherapy consisted of intravenous infusion of cisplatin 60 mg/m² on day 1 plus 5-fluorouracil 750 mg/m² on days 2-5 during the first and fifth weeks of radiotherapy. Chemotherapy was administered when leukocyte count was greater than 3000/mm³, platelet count greater than 150,000/mm³ and serum creatinine level less than 1.5 mg/dl.

Toxicity was evaluated in all patients. No patients received pre-operative brachytherapy. Physical and vaginal- pelvic examination together with abdominal-pelvic MRI were repeated 4 weeks after the end of concomitant chemoradiation for the evaluation of clinical response (according to RECIST criteria [20]) and for the planning of surgical treatment. After chemoradiation, laparotomic radical hysterectomy and pelvic lymphadenectomy were performed. If common iliac nodes were positives at frozen section, para-aortic lymphadenectomy below the level of inferior mesenteric artery was also performed. Pelvic exenteration was performed in the presence of bladder involvement. At the end of surgery and before abdomen closure IORT was delivered on bilateral pelvic sites, including the surgical resection margin of parametrium, the obturator fossa and external pelvic vessels. Monolateral delivery of IORT was performed if neoplasia was clearly expanding monolaterally with negative frozen-section in contralateral site. Other sites of pelvis and aortic lymphnodes were irradiated with IORT if the tissue removed was suspect at macroscopic inspection and confirmed at frozen-section. If ureters had to be freed from a cuff of neoplastic tissue (evaluated at frozen section), a pig-tail stent was inserted and ureters were included in IORT irradiation. IORT irradiation sites were marked with metallic clips larger than those utilized for lymphadenectomy in order to distinguish in-field from out-field pelvic recurrences. Complications were defined as intra-operative (bladder, ureter, bowel, vascular or nerve injuries and blood loss exceeding 500 ml), peri-operative (within 30 days from surgery) and post-operative (after 30 days from surgery), and described according to Chassagne [21]. Three different categories of pathological responses were determined: complete response (no evidence of tumor), partial microscopic response (only microscopic foci) and partial macroscopic response (gross persistent disease). Partial microscopic or macroscopic responses were classified by either only cervical or outside the cervix (parametrium, lymph nodes and pelvic tissue).

Follow-up

Postoperative management was individually established on the basis of histological findings on surgical samples, patient age and general conditions, after discussion of the options with the patient

132 Patients were periodically followed up with physical and gynecological examination,
133 complete blood count and blood chemistry every 3 months for the first two years and every
134 six months thereafter. Pelvic MRI and abdominal CT were performed every 6 months for
135 the first two years and every 12 months thereafter.

136 Pelvic recurrences were classified as in-field (IFR) or out-field (OFR) if they occurred
137 within or outside the IORT irradiation field. Distant recurrences (DR) were noted if they
138 occurred outside the pelvis.

139 *Statistics*

140 Chi-square test was used for discrete and binomial data. Progression-free and overall
141 survivals were estimated by the product limit method of Kaplan and Meier, and survival
142 curves were compared using the log-rank test. Cox's proportional hazard regression model
143 was used to assess the relationship between survival data and covariates. Difference was
144 considered significant if $P < 0.05$. Disease free survival (DFS) and overall survival (OS)
145 were calculated from the date of surgery to the date of relapse and to the date of death or
146 last follow-up, respectively.

RESULTS

Chemoradiation Treatment

The clinical-radiological reassessment after the end of concomitant chemoradiation showed a clinical complete response in 2/42 (5%) patients, and a partial response in 23/42 (54%), with an overall response rate of 59%. Toxicity due to chemoradiation was evaluated in all 42 patients. Hematological toxicity was grade 1-2 in 38 patients (90%) and grade 3-4 in 2 (5%). Grade 1-2 and grade 3-4 gastrointestinal toxicity occurred in 22 (52%) and 5 (12%) patients, respectively. Two patients developed grade 1-2 neurotoxicity (5%).

Surgical Treatment

Four out of the 42 initial women did not undergo surgery, three because of disease progression and one for refusal. Of the 38 patients who underwent surgery, after a median of 38 days (range from 15 to 73) from the completion of chemoradiation, three did not receive radical surgery because of unresectable tumor extended to pelvic wall (two patients) or massive intraoperative hemorrhage (one patient). Thirty-five women underwent laparotomic radical hysterectomy (classified according to Piver's nomenclature) with pelvic lymphadenectomy: 5 (14%) had type 2 radical hysterectomy, 21 (60%) had type 3 radical hysterectomy, 6 (17%) type 4-5 radical hysterectomy, and 3 (9%) had anterior exenteration. Systematic pelvic lymphadenectomy was performed in all patients with a mean of 19.8 lymph nodes removed (range from 12 to 31). Para-aortic lymphadenectomy was performed in 7 patients with a mean of 6 lymph nodes (range from 3 to 9). The mean operative time duration was 303 minutes (range from 230 to 490).

IORT Treatment

The characteristics of the 35 patients that completed the planned combined treatment RT-CT followed by surgery and IORT are reported on Table 1. IORT was delivered to bilateral pelvic wall in 29 (82.9%) patients, to mono-lateral pelvic wall in 4 (11.3%), to bilateral pelvic wall and central pelvis in one patient (2.9%) and to bilateral pelvic wall and para-

177 aortic area in one patient (2.9%). As far as IORT is concerned, the mean delivered dose
178 was 11 Gy (range from 10 to 15 Gy) and mean diameter of irradiation field was 6.3 cm
179 (range from 5.7 to 8.3 cm).

180

181

182 *Complications*

183 The only major intraoperative complication was the section of the right obturator nerve
184 infiltrated by a massively enlarged lymph node. The nerve was repaired immediately with
185 no sequelae. Twelve patients had an intraoperative blood loss greater than 500 ml and 8
186 of them required blood transfusion. In one patient an intraoperative hemorrhage did not
187 allow radical surgery and the delivery of the scheduled IORT. Peri-operative and post-
188 operative complications are reported in Table 2. Mono-or bilateral ureteral stents were
189 placed in 7 patients. Five of them had undergone a pre-operative nephrostomy for the
190 presence of hydronephrosis, whereas in 2 patients a pig tail stent was inserted after the
191 ureter was freed from fibrotic tissue with injury of ureteral serosa. Only one ureter was
192 included in IORT field. Three patients who underwent anterior exenteration had their
193 ureters sectioned on tumor-free tissue and were not included in IORT field. All three
194 ureteral fistulae occurred in the first 12 patients when we used to insert the stents through
195 ureteral incision. Because of this complication, subsequently catheters were inserted
196 through cystostomy. Deep venous thrombosis, developed in 9% of the patients, were
197 managed with high dosage of low molecular weight heparin without any embolic
198 complications (assessed by lung CT and scintigraphy).

199 The mean hospital stay was 22.1 days (range from 9 to 89). Five patients with long term
200 hospital stay were discharged and re-admitted many times for treatment-related
201 complications.

202 *Pathological Findings*

203 Pathological findings are reported on Table 3. No patient had positive surgical margins. In
204 patients with microscopic cervical residue only 4/14 of them (28.6%) had residual
205 infiltration of less than 5 mm from surface of cervical epithelium; none of these four women
206 had residual disease outside cervix. The others 10 patients had multiple foci of residual
207 tumor throughout the cervical stroma; five of them (50%) had also positive parametrium.
208 Nine patients (26%) had positive pelvic nodes within field of pre-surgical irradiation. Three
209 out of seven (43%) patients with para-aortic lymphadenectomy had positive aortic nodes,
210 and one had positive inguinal nodes.

211 *Post-operative treatment*

212 Post-operative adjuvant treatment consisted of vaginal brachithery in 4 patients,
213 chemotherapy with different agents in 8 patients, and brachithery plus chemotherapy in
214 one patient.

216 *Follow-up*

218 At the time of the present analysis, 17/35 (48%) patients were alive but developed a
219 relapse with a median of 22 months and 15/35 (43%) patients died of disease with a
220 median of 33 months; 3/35 (9%) patients were alive and free of disease.

221 Recurrent disease was pelvic in 10 patients, pelvic plus distant in 3 (one in the lung and
222 two in aortic nodes), and distant alone in 4 (one in the lung, two in para-aortic nodes, one
223 in neck nodes). As far as the 13 pelvic failures are concerned, 4 recurrences were IFR and
224 9 were OFR.

225 As a whole, 4 out of 35 (11%) patients with Locally Advanced Cervical Cancer (LACC) and
226 treated with IORT experienced an IFR. All the recurrences occurred within 24 months.

227 Three of the 15 significantly, due to septic pelvic complications, were computed as
228 disease related.

229 *Statistical Evaluation*

230 In the group of 35 patients treated with radical surgery and IORT, 5-year DFS and 5-year
231 OS were 46% and 49%, respectively (Figure 1 for OS) with significantly better OS in
232 patients with no residual disease or disease limited to cervix after chemoradiation.

233 Both in univariate (log-rank test) and multivariate analysis (Cox proportional hazard model)
234 DFS and OS were significantly associated only with residual disease outside the cervix:
235 HR=0.13 (95% CI=0.04 - 0.44, $p<0.002$) and HR=0.15 (95% CI 0.03 - 0.65, $p<0.02$)
236 respectively. Stage (\geq Stage 2), age (more or less than 50 years), and tumor diameter
237 (greater or less than 4 cm) were not significantly correlated with DFS and OS (data not
238 shown). These figures were similar both in the whole group of 42 patients with the
239 intention to treat analysis and in the group of 35 patients who underwent radical surgery
240 and IORT.

DISCUSSION

Concurrent chemoradiation represents the gold standard for the treatment of patients with LACC[22]. However, further clinical investigation is strongly recommended to identify new treatment strategies aimed to maximize the local control and to improve overall survival. In this context, the integrated use of three-modality treatment (radiotherapy, chemotherapy and surgery) was tested in this clinical setting [18,23-25]. Some authors have also added IORT procedure in their treatment protocol [26]. Several studies have enrolled a variable proportion of stage Ib2 patients, a sub-set of advanced cervical cancer that usually experience a more favorable prognosis than women with extra cervical extension of disease. Therefore in the present study we decided to recruit only patients with extra-cervical tumor (and a less favorable prognosis within all LACC patients) to test if a multimodality treatment including IORT could improve both local control and long-term clinical outcome. Our set of patients includes both stage II cancers, for whom the standard treatment is exclusive concomitant chemoradiation, and stage III patients for whom different treatment approaches seem to have similar dismal results [12, 27] although a recent paper[19] seems to disclose new perspectives in stage III patients treated with surgery following neo-adjuvant chemoradiation.

Complications

Both chemoradiation related side effects and intra-operative complications were acceptable and comparable to those reported in the literature [5,23]. Less than 12 % of women experienced a grade 3-4 toxicity due to chemoradiation, 23% had a blood loss requiring transfusion, and one woman had obturator nerve section. On the other hand, peri-and post-operative complication rates were relatively high, especially as far as lymphocele (21%), pelvic sepsis (14%), ureteral fistulae (8%) and deep venous thrombosis (9%). The mean hospital stay was of 22 days, in excess of that reported by other authors in comparable surgical settings [18]. This long hospital stay was due to treatment complications and to the fact that patients were not discharged until lymphorrhea from drainage was less than 100 ml per day. Three of the 15 deaths were due to septic pelvic complications but were attributed to the disease in survival calculations. The high rate of surgery-related complications is due to the combination of high radiation dose and aggressive surgery, in agreement with the data of Houvenaeghel *et al.* [28] who reported a

complication rate of 32% after radical hysterectomy compared with 12% after simple hysterectomy.

Response characteristics

In our population, the clinical overall response rate to chemoradiation was 59%, and the optimal pathological (complete plus partial microscopic) response rate was 45.8%, slightly lower than that reported following chemoradiation (61-73%) by other authors [23,25,28]. The different pathological response rates may be partly dependent on the heterogeneity of patient populations and treatment modalities [18,23,25,28]. In our study, the extended pelvic field external irradiation dosage was 10-20% higher, and cisplatin dose intensity was 25-40% lower when compared to those used by other authors, and brachytherapy was not administered. Moreover, patients with stage Ib2 cervical cancer were not included in the present analysis, and the overall survival was unsatisfactory, albeit similar to that observed for a comparable group (stage II - IV) of patients treated with chemoradiation only in GOG 120 and GOG 165 trials [27]. The only significant variable influencing recurrence rate and survival was the presence of residual tumor outside the cervix (Figure 1 for OS) irrespective of the amount of cervical residue. The subset of 15 patients (43%) with residual tumor only within the cervix had an excellent prognosis, with 5-year cumulative survival higher than 80%. On the other hand, the 20 patients with extra-cervical tumor residue had a dismal clinical outcome, irrespective of site of residual disease (either pelvic nodes or parametrial-vaginal tissue), with a 3-year cumulative survival of only 24%. It is possible that aortic lymph nodes positivity could influence the survival figures, although all the patients were selected for absence of disease outside the pelvis by pre-treatment imaging.

Prognostic Factors

Therefore, the persistence of extra cervical residual disease after chemoradiation, even if surgically removed, is a poor prognostic factor. Although IORT improves local control of neoplasia (IFR are only 11.4% of total recurrences), local control of neoplasia does not contribute to overall survival, that is dismal in this set of patients with extra cervical LACC. It is possible that patients without residual disease outside the cervix could be conveniently treated with brachytherapy following chemoradiation as well.

Outlook

It seems that extra cervical LACC is not a local neoplasia any more. So the intensification of concurrent chemotherapy regimen (increased cisplatin dose intensity) in chemoradiation protocols and especially a more accurate selection of patients who could benefit from this combined treatment are strongly recommended for future studies in order to improve the clinical outcome and to minimize complications.

CONFLICT OF INTEREST STATEMENT

There is no direct financial interest with any company in this trial, that was supported only by Centro di Riferimento Oncologico (C.R.O) - I.R.C.S.S

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408

409

TABLE 1: Characteristics of the 35 patients who completed the study protocol

Age, mean (range)	50.0 (33-75)
BMI, mean (range)	26.1 (17.5-40.5)
Histology SCC:AC	33:2
IIA-bulky	2 (6%)
IIB	17 (48%)
III-IVA	16 (46%) (8 with nephrostomy)
Tumor volume, cm, mean (range)	4.5 (3-8)
Positive pelvic Lymphnodes At imaging	10

Legend : BMI, body mass index; SCC, squamous cell carcinoma; AC, adenocarcinoma

TABLE 2: Peri-operative and post-operative complications observed in the 35 patients who completed the study protocol

	Peri-operative	Post-operative	Total
Lymphocoele	3	3	6 (17%)
Pelvic Sepsis	2	3	5 (14%)
Urinary Infection (pyelonephritis)	3	-	3 (8.6%)
Deep Venous Thrombosis	-	3	3 (8.6%)
Ureteral Fistula	2	1	3 (8.6%)
Bladder fistula	-	1	1 (2.9%)
Ureteral Stenosis	-	3 (1 requiring nephrostomy)	3 (8.6%)
Necrotic Wound Dehiscence	2	1	3 (8.6%)

TABLE 3: Pathological results of the 35 patients who underwent radical surgery

Treatment response		Positive parametrium	Positive vagina	Positive pelvic Nodes
Cervical Complete response	12 (34%)	0%	1/12 (8%)	3/12 (25%) one also aortic positive nodes
Cervical microscopic residual disease	14 (40%)	3/14 (21%)	4/14 (29%)	1/14 (7%)
Cervical macroscopic residual disease	9 (26%)	7/9 (78%) one macroscopic involvement	2/9 (22%)	5/9 (55%) two also positive aortic and one positive inguinal nodes
	35	10 (28.6%)	7 (20%)	9 (26%)

FIGURE 1

