Yonsei Medical Journal
Vol. 33, No. 2, 1992

☐ Review Article ☐

Radiotherapeutic Management in Carcinoma of the Uterine Cervix: GOG Experience[a]

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Just when the Wertheim's hysterectomy had reached its highest technical perfection, Roentgen ray and radium were discovered in the 1890's. The early major development of radium treatment for cancer of the uterine cervix began at Radiumhemmet, Stochkholm under Forssell in 1910 and Paris, Institute du Radium under Regaud in 1913. Subsequently, Heyman first reported that their results of radiation treatment were as good as radical surgery in 1927 (Heyman, 1927).

Radiation therapy (RT) for cancer of the uterine cervix consists of intracavitary and external beam treatments, two distinct modalities with different purposes. Technical improvement from kilovoltage to megavoltage RT allows a higher tumor dose. At the same time, the development of afterloading intracavitary applicators and the gradual replacement of radium by cesium-137 have permitted more flexibility and accuracy in the administration of intracavitary therapy. Recently, computers and CT scans have facilitated the precise determination of RT doses to various points of the pelvis including tumor extension. Furthermore, parallel advances in the understanding of the natural history of this maliganancy and the patterns of failure after standard therapy have fostered a sound rational for further improvement in control of this disease.

Despite the frequent success of surgery and RT in curing cancer of uterine cervix, there remain a number of women who present with late stage cancer and a subset of early stage patients who will not be cured with standard therapy. The patterns of failure with RT are characterized by an increasing number of pelvic recurrences and distant metastatic disease associated with more advanced stages at the time of presentation (Jampolis *et al.* 1975; Kim *et al.* 1989; Perez, 1992). In the United States, the Patterns of Care study clearly demonstrated the treatment of cervical cancer to be far from uniform. However, as the radiation dosage is increased, there have been a diminution of pelvic failure in the late stage disease (Hanks *et al.* 1983). Pelvic failure as described in the literature are shown in Table 1.

This review will focus primarily on major GOG

Table 1. Carcinoma of the uterine cervix: pelvic faliure by stage

Stage	Total Pelvic failure[a](%)		
	Perez[b]	Jampolis	Kim[c]
IB	9.1	6.3	11.2
IIA	16.9	7.3	8.4
IIB	22.6	17.6	30.1
IIIB	44.6	43.1	52.3
IVA	72.0		69.0

a. Pelvic failure only+Pelvic and distant failure
b. point A dose (7000-8000 cGy for stage I-IIA, 8000-9000 cGy for stage IIB-IVA)
c. point A dose (≤ 7500 cGy for all stages)

Received May 18, 1992

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[a]Gynecology Oncology Group (GOG) is national multi-institutional cooperative group founded in 1970 and devoted solely to Gynecologic Oncology problems. GOG consists of Gynecologic Oncologists, Radiation Oncologists, Medical Oncologists, Gynecologic Pathologists, Oncology nurses and statisticians.

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efforts to improve local control and survival of cancer of the uterine cervix.

One of the earliest and simplest measures, milligram-hours, is still an integral component in the Fletcher system. GOG has been using "Point A" dose prescription in the Manchester system. For large volume disease (stage IB-bulky, IIB. III. IVA), combined intracavitary and external doses to point A and point B were 8000 cGy and 5500-6000 cGy respectively with a minimal dose of 4000-5000 cGy external pelvic irradiation.

SURGICAL AND RADIOLOGICAL STAGING STUDIES

The conventional surgical and radiotherapeutic modalities limit treatment to the pelvis and nearby structures so that those patients who initially have disease outside of this area of treatments are destined to fail. Therefore, the first GOG protocol was on the surgical staging of periaortic lymph nodes.

GOG protocol 19 (Lagasse *et al.* 1980)

This protocol addresses the surgical-pathologic staging of periaortic lymph nodes in 290 patients with invasive cancer of the cervix. The relationship beween clinical stage and positive periaortic lymph nodes in the literature and this study is shown in Table 2. By means of surgical staging, a substantial portion of patients with cervical cancer have been found to have disease outside the usual pelvic field of radiation treatment. In the absence of an accurate non-invasive technique for determining nodal metastases, surgical staging in being incorporated into the design of all GOG studies except GOG protocol 4.

GOG protocol 63 (Heller *et al.* 1990).

The use of lymphangiography (LAG), computerized tomography (CT) and ultrasonography (US) to evaluate extra pelvic metastasis has been described. However, these studies often report conflicting results for the specificity or sensitivity.

Thus, GOG protocol 63 prospectively randomized use of CT, LAG and US to evaluate the periaortic lymph nodes before sugical staging confirmation in two hundred sixty-four patients. This study showed that LAG was the most reliable non-invasive examination although it is not highly specific, but is relatively sensitive (Table 3). CT did not appear to have the accuracy reported by others.

Table 3. Diagnostic procedures and tissue confirmation

Procedure	Histology/cytology	
	Positive Periaortic nodes	Negative Periaortic Nodes
Sonogram		
Positive	10(18.5)[a]	2(1.3)
Negative	44(81.5)	158(98.7)
CT scan		
Positive	21(34.4)	8(4.2)
Negative	40(65.6)	184(95.8)
Lymphangiogram		
Positive	44(78.6)	50(27.0)
Negative	12(21.4)	135(73.0)

a=Number(%)

Table 2. Combined data in literature and GOG study showing positive periaortic node metastasis

	Stage			
	IB	IIA	IIB	IIIB
Sudarsanam	11/ 53(7%)	3/21(14%)	4/22(18%)	3/16(19%)
Nelson			3/31(16%)	13/28(46%)
Piver			6/46(13%)	18/49(36%)
Wharton	0/ 21(0%)	0/10(0%)	10/47(21%)	14/42(33%)
GOG #19	8/143(5%)	4/22(18%)	19/58(33%)	19/61(31%)
Total	19/319(6%)	7/53(15%)	42/214(19%)	74/216(34%)

Until better methods of noninvasive evaluations are developed, they concluded that surgical staging remains the only definitive means of determining metastasis in the periaortic lymph nodes.

Early stage cancer of the uterine cervix

The primary treatment of stage I and stage IIA cervical cancer involves surgery and/or radiation therapy (Shingleton *et al.* 1988). Surgical treatment is preferred in younger patients in whom preservation of ovarian and vaginal function is desired.

Stage IB cancer of the cervix consists of a wide range of lesions, from micro-invasion to bulky tumor. In surgical management of stage IB cancer of the cervix, Several authors have attempted to identify poor prognostic factors (Piver *et al.* 1975; Van Nagell *et al.* 1978). GOG retrospective surgical and pathological analysis has confirmed that disease-free survival correlated strongly with the depth of tumor invasion, clinical tumor size and capillary/lymphatic space involvement (Delgado *et al.* 1989). A significant decrease in five-year survival rate has been found from 96% to 60% when there is pelvic node involvement (Morrow *et al.* 1980). Most investigators currently recommend postoperative whole pelvis irradiation for patients with positive lymph nodes, although the true impact of this therapy has been difficult to verify.

In radiotherapy management of stage IB cancer of the cervix, bulky disease or the so called "barrel shaped" cervix has a higher local failure. This has been variously defined as greater than 2.0 cm to greater than 6.0 cm. The patterns of care study defines cervical lesions more than 4.0 cm in greatest diameter as bulky disease. Management of this entity is controversial but one method is definitive radiation therapy alone (Perez *et al.* 1985). An alternative method is planned presurgical radiation therapy consisting of combination of external beam irradiation and at least one intracavitary application followed by extra-facial hysterectomy (Fletcher *et al.* 1978).

GOG protocol 71

This study is a phase III randomized comparison of radiation therapy alone versus radiation therapy plus adjuvant extra-facial hysterectomy for the patient with "bulky" stage IB cancer of the cervix. This study radomized 263 patients with tumor greater than 4.0 cm in size between October, 1984 and November, 1991. The final results will be available within a few years.

GOG protocol 92

Although the majority of patients with stage IB cancer of the cervix are cured with radical hysterectomy and pelvic lymphadenectomy, the 20 % disease-relate mortality in these patients has not improved during the last two decades. Risk factors for local failure are positive pelvic lymph node (Bleker *et al.* 1983), positive surgical margin (Kim *et al.* 1988), positive parametrial involvement (Inoue, 1984), tumor size, the depth of tumor penetration into the cervical stroma, vascular or lymphatic channel involvement and corpus extension (Gauthier *et al.* 1985; Creasman *et al.* 1986).

This GOG protocol 92 is a phase III randomized comparison with or without postoperative pelvic RT is patients with "intermediate risk" groups after radical hysterectomy and pelvic lymphadenectomy for stage IB cancer of the cervix. Intermediate risk factors being evaluated in this protocol are depth of penetration, tumor size and vascular or lymphatic channel involvement. This study, initiated in 1988, is still in progress.

GOG protocol 109

Although external beam RT can eradicate microscopic tumor in regional pelvic lymph nodes, retrospective studies have failed to demonstrate a survival advantage in patients treated with RT. This finding suggests that the decrease in pelvic recurrence achieved may be offset by an increase in extrapelvic or distant metastasis. GOG 109 is a phase III randomized comparison between continuous infusion 5-fluorouracil (5-FU) and bolus CisPlatin as an adjunct to RT versus RT alone in "high risk" patients with stage IB and stge IIA cancer of the cervix, following radical hysterectomy and node dissection. High risk factors are positive pelvic lymph involvement. The goal of this study is to determine whether the combination of CisPlatin and 5-FU can improve progression-free interval and survival in high risk patients receiving postoperative RT after radical hysterectomy and node dissection.

LATE STAGE CANCER OF THE CERVIX

The inability to control the tumor in the pelvis for stage IIB, III, and IVA is still a significant concern. As the radiation dosage is increased, there has been a diminution in the incidence of pelvic failure (Kim

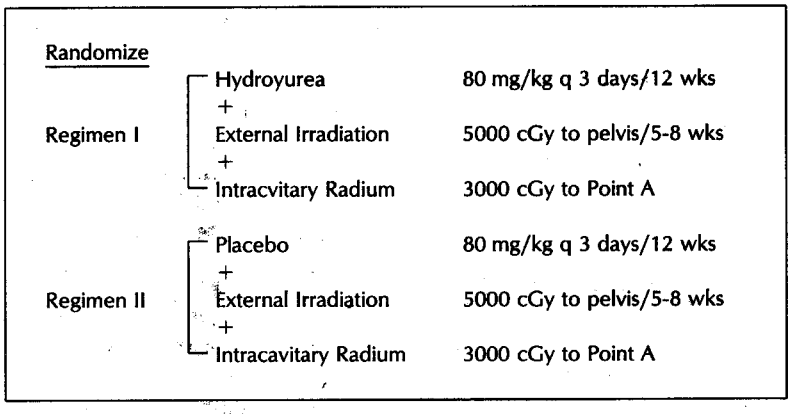

Fig. 1.

Table 4. Response by therapy

Response category	Treatment				Total
	Hydroxyurea		Placebo		
	No.	(%)	No.	(%)	
Stable disease	1	(2.1)	7	(16.3)	8
Partial response	9	(19.2)	7	(16.3)	16
Complete response	32	(68.1)	21	(48.8)	53
Progression	5	(10.6)	8	(18.6)	13
Total	47	(100.0)	43	(100.0)	90

et al. 1989; Perez *et al.* 1992) but, along with this, an increase in complications. The combination of RT and surgery has not significantly improved tumor control and survival, except in a very selected group of patients, such as those with barrel-shaped cervix. Opportunities for clinical research in these areas are multiple, including altered fractionation, interstitial brachytherapy, combination treatment with a radiation sensitizer and/or chemotherapy.

In an attempt to maximize the effectiveness of RT, GOG explored a series of combination treatment programs with cytotoxic chemotherapy and/or radiation sensitizer since 1971.

GOG protocol 4 (Hreshchyshyn *et al.* 1987)

This study is a phase III randomized comparison between hydroxyurea versus placebo, combined with radiation for stage IIIB and IVA carcinoma of the cervix (Fig. 1). The hydroxyurea kills cells in the S phase of the cell cycle, and prevents cells in G_1 from entering the S phase. This leads to a synchronization at the sensitive G_1/S interphase when radiation is delivered. In addition, Hydroxyurea prevents the repair of sublethal radiation damage.

This GOG protocol concluded that although hematologic toxicity were more common and more severe in patients who received hydroxyurea, pelvic control was significantly better in the group of patients receiving hydroxyurea (Table 4). Survival and duration of progression-free interval were significantly better between the two groups, favoring hydroxyurea. However, this study has been criticized on several grounds: Of 190 patients randomized, only 97 (51%) were considered evaluable for survival analysis. The minimum dose to point A was low

for late stage of disease(7000 cGy). Lastly, the 3-year Disease-Free survival (DFS) was only 13% in the control Arm (DFS was 26% in the Hydroxyurea Arm).

GOG protocol 24 (DiSaia *et al.* 1987)

This study is a phase III study comparing RT alone versus RT plus immunotherapy (intravenous corynebacterium parvum) in stage IIB, III, IVA cancer of the cervix. In this study, no therapeutic value was demonstrated by combining C. parvum therapy with standard RT.

GOG protocol 56 (Stehamn *et al.* 1988).

This study is a phase III randomized trial of hydroxyurea versus misonidazol adjuvant to RT in stage IIB, III, IVA cancer of the cervix. Misonidazol, the first of a new group of radiosensitizers, sensitizes hypoxic tumor cells through its electron affinity. Although it is inconclusive that hydroxyurea with RT is superior to misonidazol with the RT, it appears that hydroxyurea is the more appropriate potentiator in patients with bulky cervical cancer.

GOG protocol 85

This study is a phase III randomized comparison of hydroxyurea versus 5-FU continuous infusion and bolus CisPlatin as an adjunct to RT in patients with stage IIB, III, and IVA carcinoma of the cervix. 5-FU and CisPlatin have been used in an attempt to increase the effectiveness of RT in squamous cell carcinoma of the cervix (Wade *et al.* 1984), head and neck, (Byfield *et al.* 1984) and esophagus (Leichman *et al.* 1984). The purpose of this study is to determine whether hydroxyurea or the combination of 5-FU and CisPlatin is superior as a potentiator of RT in advanced cervical cancer. Patient accrual ended in December, 1990 and final results should be available within a few years.

PERIAORTIC METASTASIS

The patterns of spread in cervical cancer are quite predictable. With increasing stage and volume of local disease, there is an increased likelihood of regional spread to pelvic lymph nodes followed by metastases to higher lymph node groups along the aorta. Previous reports (Lagasse *et al.* 1980) have confirmed that the incidence of positive periaortic nodes was approximately half of the pelvis node metastasis at each stage.

Although long term survival with metastatic periaortic disease is poor, most important influencing the likelihood of cure in patients with periaortic metastases are the volume of pelvic and periaortic disease. The median survival of 98 patients treated with 4500 cGy for periaortic metastasis was 15.2 months with a survival probability of 25% at 3 years. Recurrences were divided approximately equally between the pelvis and distant sites (Berman *et al.* 1984).

GOG protocol 59 (Varia *et al.* 1986)

This study is a phase III extended RT and hydroxyurea program followed by randomized comparison of CisPlatin versus no further chemoterapy in patients with carcinoma of the cervix with metastasis to high common iliac and/or periaortic lymph nodes. The results from this study indicate that even in the young patients population with favorable performance status, post radiation systemic chemotherapy after extended field RT and hydroxyurea was not feasible due to bone marrow toxicity.

Two randomized studies addressed "elective" irradiation of the periaortic node in squamous cell carcinoma of the uterine cervix. The Radiation Therapy Oncology Group (RTOG) study Rotman (*et al.* 1990) randomized 367 patients to receive either pelvic irradiation or pelvic plus periaortic radiation for stage IB/IIA with primary tumor measuring 4.0 cm or greater and stage IIb. The patients with clinically apparent or histologically involved periaortic nodes were excluded from this study. The difference in absolute survival was statistically significant: The periaortic group showed a 66% 5-year survival and the pelvic group 55%. The 2- and 5-year survival differences were more pronounced in stage IB and stage IIA with the periaortic group at 89% and 65% and the pelvic group at 66% and 51% respectively. The recently published study conducted by the radiation therapy cooperative group, European Organization for Research and Treatment of Cancer (EORTC) remains the only other randomized study that compared pelvic alone versus "elective" periaortic irradiation in stage I with positive pelvic lymph nodes, IIB and III cancer of the cervix (Haie *et al.* 1988). This EORTC trial included stage III patients where the RTOG trial did not. In the EORTC study, there was a significant reduction in clinically evident periaortic node metastases in the group assigned to "elective" periaortic irradiation. However, no statistic difference of NED survival was found between these two groups at 4 years for all stages.

These studies strongly support the beilef that extended field radiation is of greatest benefit when applied to stage I and stage II patients at increased risk for microscopic or subclinical deposits within regional lymph nodes. When tumor burden increased from stage IIb to stage III, the risk/benefit ratio of extended field radiation declined.

FUTURE STUDIES

Several pilot studies are ongoing for future GOG studies.

A. A phase I evaluation of multiple daily fraction radiation with hydroxyurea or 5-FU and Cis-Platin (stage IIB-IVA).
B. A phase II evaluation of intra-arterial CisPlatin infusion and irradiation (stage IIB-IVA).
C. Concurrent alpha-interferon and irradiation (stage IIB-IVA).
D. Drugs as modulators of RT such as hypoxic and non-hypoxic cell sensitizers (stage IIB-IVA).
E. Neoadjuvant chemotherapy followed by radical hysterectomy and pelvic lymphadenectomy (stage IB bulky tumor).
F. High dose rate brachytherapy, phase I/II trial (all stages).

Because of the high incidence of distant metastasis in patients with late stage cancer of the cervix, it is imperative to develop effective systemic adjuvant chemotherapy in order to improve the prognosis of these patients. Lastly, multi-modality programs utilizing a combination of surgery, radiation therapy, chemotherapy and biologic response modifiers through multi-institutional cooperative groups should improve the survival rate in high risk cervical cancer patients.

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