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Advances in Cervical Cancer Management from North American Cooperative Group Clinical Trials

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Despite effective screening methods for detecting pre-malignant diseases of the cervix, cervical cancer remains a leading cause of cancer mortality in women globally. There has been a dramatic decline in the age adjusted death rate from cervical cancer in the United States, where cervical cancer has declined from the leading cause of cancer mortality in women prior to 1940 to a point where it is a relatively uncommon cause of cancer mortality today. Despite these advances in screening and early detection reported in the United States, intraepithelial disease detection rates in many non-industrialized countries remain low because screening programs are generally lacking. As a result most cancers detected in many underdeveloped areas of the world are advanced at diagnosis. Furthermore, in such countries there may be inadequacies in physicians trained in the most effective means of treating cervical cancer, technical support required for the effective delivery of radiation therapy or the administration of chemotherapy, and modern equipment required for optimal treatment with radiation therapy. Thus cure rates for women with cervical cancers in many areas of the world remain low.

INTRODUCTION

The American Cancer Society estimates that 13,000 new cases of cervical cancer will be diagnosed and only 4,100 resultant deaths will occur in the United States in 2002.[1] As expected, the

dramatic decline in the cancer death rate in the United States has been accompanied by an equally dramatic rise in the detection of pre-nvasive disease. Concurrent with effective screening programs in the United States has been a clinical research effort performed through cooperative clinical trials which has markedly advanced our understanding of prognostic factors associated with cervical cancer while identifying more effective treatment strategies for cervical cancer patients. These cooperative group trials have been performed largely through the Gynecologic Oncology Group (GOG), the Southwest Oncology Group (SWOG) and the Radiation Therapy Oncology Group (RTOG), with most participating institutions located within the United States. This manuscript will address some of the most important results of these clinical trials over the past twenty years with a particular focus on recent advances in the treatment of high risk patients with multimodality regimens that include platinum based chemotherapy. As resources needed for the care of women with cervical cancer become more widely available throughout the world, it is likely that the efforts of these cooperative group trials will add substantially to the probability of curing thousands more of these women.

North America Cooperative Group Clinical Trials

The first large clinical trial performed by a cooperative group in North America addressed prognostic features associated with cervical cancer and was opened for entry by GOG in 1981. Protocol 49 registered 1120 patients, 732 of whom

had squamous cell cancers with Stage I disease (clinically confined to the cervix) and a depth of invasion greater than 3 mm (Stages IA2 and IB). It is noteworthy that this trial was performed prior to changes in staging criteria adopted by FIGO in 1994 which further subdivided Stage IB disease based on tumor size into Stage IB1 and IB2[2] (Table 1). As expected, the probability of achieving a durable disease free status in patients managed by radical hysterectomy and bilateral pelvic lymphadenectomy correlated significantly with depth of tumor invasion, clinical tumor size, capillary lymphatic space involvement, tumor grade and occult parametrial extension.[3] Interestingly, patient age and uterine extension of the tumor in this trial did not influence the disease free interval significantly. Independent prognostic factors identified by multivariate analysis as being associated with recurrence and death were clinical tumor size of the primary tumor (≥ 3 cm vs. <3 cm), capillary lymphatic space involvement, and depth of tumor invasion into the cervical stroma. This latter factor was seen when depth of infiltration was divided into inner, middle, and outer thirds of the cervix, and also when determined by measuring the depth of infiltration in millimeters. To illustrate the impact of tumor size, the investigators reported that patients with squamous cell cancers who had 4-cm tumors experienced a risk of recurrence 2.9 fold greater than those whose cancers were occult. Likewise, capillary lymphatic space involvement in these patients increased the risk of recurrence by 70% over cancers without this feature. Remarkably, pelvic lymph node status did not prove to be an independent prognostic factor.[3] When considering

Table 1. FIGO Staging System in Cervical Carcinoma

Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded).
Stage IA	Invasive cancer identified only microscopically. All gross lesions even with superficial invasion are Stage IB cancers. Invasion is limited to measured stromal invasion with maximum depth of 5.0 mm and no wider than 7.0 mm.
Stage IA1	Measured invasion of stroma no greater than 3.0 mm in depth and no wider than 7.0 mm.
Stage IA2	Measured invasion of stroma greater than 3.0 mm in depth and no greater than 5.0 mm in depth and no wider than 7.0 mm.
Stage IB	Clinical lesions confined to the cervix or preclinical lesions greater than IA.
Stage IB1	Clinical lesions no greater than 4.0 cm in size.
Stage IB2	Clinical lesions greater than 4.0 cm in size.
Stage II	The carcinoma extends beyond the cervix but has not extended to the pelvic wall. The carcinoma involves the vagina but not as far as the lower third.
Stage IIA	No obvious parametrial involvement.
Stage IIB	Obvious parametrial involvement.
Stage III	The carcinoma has extended to the pelvic wall. On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. The tumor involves the lower third of the vagina. All cases with a hydronephrosis or nonfunctioning kidney are included unless they are known to be due to other causes.
Stage IIIA	No extension to the pelvic wall.
Stage IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney.
Stage IV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum. A bullous edema as such does not permit a case to be allotted to Stage IV.
Stage IVA	Spread of the growth to adjacent organs.
Stage IVB	Spread to distant organs.

independent prognostic factors that influenced the risk of pelvic lymph node spread, only capillary lymphatic space involvement, depth of infiltration, parametrial involvement, and patient age were identified by multivariate analysis.[4]

GOG Protocol 49 was closed to patient enrollment in 1984 and underwent data analysis in 1988. Based upon the findings of this trial, GOG initiated a prospective randomized study (GOG Protocol 92) of adjuvant pelvic radiotherapy in patients at intermediate risk of treatment failure with surgery alone based upon the prognostic features identified in Protocol 49. Specific risk factors for treatment failure which were considered in this trial included depth of stromal invasion (greater than 1/3), capillary lymphatic space involvement and large clinical tumor diameter. Patients with positive capillary space involvement who also had either outer third infiltration, middle third infiltration with a tumor of at least 2-cm diameter, or inner third infiltration with a tumor of at least 5-cm diameter were eligible for enrollment. Additionally, patients without capillary space involvement were eligible if their tumors invaded into the outer 2/3 of the cervical stroma and were at least 4 cm in diameter. Women with lymph node metastasis were excluded from this trial. Of the 277 women who underwent radical hysterectomy with bilateral pelvic lymphadenectomy and were enrolled, 137 were randomized to receive external beam radiotherapy (46 to 50.4 Gy) and 140 received no adjuvant radiotherapy. This trial demonstrated a 47% reduction in the risk of recurrence in those patients treated with adjuvant radiotherapy as compared with surgery alone (p=.008).[5] The 2-year recurrence free rate in the group treated with surgery plus radiation therapy was 88%, vs. 79% in the surgery only treatment group. As expected, Grade 3 and 4 adverse events occurred more commonly in the radiation therapy arm of the trial (6% vs. only 2.1% in the surgery only treatment group). One patient who received radiation therapy died from sepsis associated with the development of a vesicovaginal fistula. The conclusion from this study was that adjuvant radiotherapy, in Stage I lymph node negative patients with various adverse prognostic features undergoing primary surgical management by

radical hysterectomy and bilateral pelvic lymphadenectomy, produced a significant reduction of cancer recurrence and had an acceptably low morbidity when compared with treatment by surgery alone.[5]

When GOG Protocol 92, which was carried out by the member institutions of GOG in conjunction with SWOG, was closed to enrollment, SWOG opened a clinical trial to study the possible role of adjuvant cisplatin based chemotherapy in the treatment of poor prognosis Stage IA2, IB, and IIA cervical carcinoma. Eligible patients were defined as those with pelvic lymph node metastasis, positive parametrial extension or a positive surgical margin. All patients had undergone a type 3 radical hysterectomy with bilateral pelvic lymphadenectomy.

Collaboration between SWOG, GOG and RTOG enabled the enrollment goals to be met in a timely fashion. Of the 268 patients enrolled in this trial, 243 were assessable, including 127 treated by means of radiation therapy with chemotherapy and 116 with radiation therapy alone. Radiation therapy was delivered to the whole pelvic area as 49.3 Gy over 29 fractions in six weeks. Those patients treated with chemotherapy received 70 mg/m^2 cisplatin and a 96-hour infusion of Fluorouracil, 1000 mg/m^2 per day every 3 weeks for 4 cycles beginning with the initiation of radiation therapy.

Results of this trial demonstrated that these early stage, cervical cancer patients with poor prognosis achieved a significant improvement in 4-year progression free survival when adjuvant chemotherapy was added to pelvic radiotherapy; 80% for radiotherapy plus chemotherapy, versus 63% for radiotherapy alone (p=.003). Furthermore, the projected overall survival at 4 years was 81% for the chemotherapy-containing regimen vs. 71% for the treatment arm which did not include chemotherapy (p=.007). As expected, gastrointestinal and hematologic toxicity was greater in the chemotherapy treatment group reflecting the characteristic toxicities associated with both of these agents.[6] Because this SWOG clinical trial included patients with positive lymph nodes and because GOG 92 excluded these patients, it is not possible to compare the treatment results between the two protocols directly. Nevertheless, the

authors suggest that adjuvant radiation therapy has a role for patients at high risk of recurrence and that the addition of concurrent cisplatin based chemotherapy to radiation therapy significantly improves progression free and overall survival for these high risk, early stage, cervical cancer patients following radical hysterectomy and pelvic lymphadenectomy.

Women with Stage IB2 cervical cancers provide a particular challenge to the treating physician. Treatment has not been standardized and often includes either radical hysterectomy with bilateral pelvic lymphadenectomy commonly followed by adjuvant radiotherapy, or radiation therapy with or without post treatment hysterectomy. The lack of standardization and frequent use of multimodality therapy probably reflects the increased risk of central failure associated with single modality (either surgery or radiation therapy alone) in addition to the high risk of occult metastatic disease to the pelvic and periaortic lymph nodes. Because of this dilemma GOG developed a clinical trial (GOG 123) in an effort to standardize treatment for these patients. In view of the high failure rate with single modality therapy and with evidence that adjuvant cisplatin based chemotherapy improves survival in high risk, early stage, cervical cancer patients, GOG 123 was a clinical trial of conventional radiotherapy with or without cisplatin based chemotherapy followed by a total abdominal hysterectomy and bilateral salpingooophorectomy for women with Stage IB2 cervical cancer. Eligible patients had no radiologic evidence of lymphadenopathy on CT scanning or lymphangiography. Also eligible were patients with enlarged or suspicious appearing lymph nodes by imaging study but with no evidence of metastatic cancer found on fine needle aspiration or histologic evaluation of these nodes. All patients underwent external beam radiotherapy delivered via the four field technique with X-Ray accelerators of at least 4-MEV photons delivered in 1.8 to 2.0 Gy fractions 5 days weekly over a period of 4.5 to 5 weeks for a total dose of 45 Gy. Low dose brachytherapy was performed in one or two intracavitary applications providing a cumulative dose of 75 Gy to point A and 55 Gy to point B. Patients who were randomized to receive chemotherapy were given cisplatin 40 mg/m^2

intravenously once weekly beginning concurrently with the start of external beam radiotherapy of a total dose not exceeding 70 mg per week for a maximum of 6 doses. All patients underwent extrafascial hysterectomy 3 - 6 weeks after completion of radiotherapy.

As with GOG 109, a significant survival advantage was reported for the treatment arm in GOG 123 which included cisplatin chemotherapy. The relative risk of progression in patients treated with chemotherapy and radiation followed by surgery versus patients treated with radiation alone followed by surgery was .51 ($p < .001$). Similarly, the relative risk of death in the chemotherapy arm versus the treatment arm which did not contain chemotherapy was .54 ($p=.008$).[7] As expected, both hematologic and GI toxicity were significantly higher in the chemotherapy arm reflecting the typical toxicities associated with cisplatin. Grade 3 and 4 adverse hematologic effects occurred in 21% of enrollees in the chemotherapy arm vs. 2% in the group that received no chemotherapy. Similarly, adverse gastrointestinal effects occurred in 14% vs. 5% of enrollees, respectively. This trial also permitted the assessment of prognostic factors in this group of patients. The authors reported that the size of the tumor as assessed by physical examination and the histologic grade of the tumor were both significant prognostic factors in this patient population. They further concluded that the addition of weekly cisplatin infusions to pelvic radiotherapy followed by hysterectomy in patients with Stage IB2 disease significantly reduces the risk of recurrence and death.[7]

It is noteworthy that other treatment approaches for patients with high-risk, early stage, cervical cancer are being investigated. In particular, there has been great interest in a possible role for neoadjuvant chemotherapy followed by radical hysterectomy or radiotherapy, depending upon the initial response to chemotherapy. This interest has been stimulated by the pioneering work of Sardi et al.[8] Based upon these initial efforts, GOG developed protocol GOG 141 to investigate neoadjuvant chemotherapy in patients with bulky Stage IB2 and IIA cervical cancer in the cooperative group setting. This clinical trial was closed to enrollment in July 2001 and data

analysis likely will be forthcoming.

In view of the remarkable impact of cisplatin based chemotherapy on survival in high and intermediate risk, early stage, cervical cancer patients, it is not surprising that a similar effect has been demonstrated in women with more advanced disease. RTOG studied women of all ages with Stage IIB through IVA cervical cancer in addition to earlier stage patients with tumors of at least 5 cm diameter or smaller lesions with biopsy proven metastasis to pelvic lymph nodes. Patients with periaortic lymph node metastasis were excluded from eligibility. Assessment of the periaortic lymph nodes was accomplished either based on bipedal lymphangiography or retroperitoneal surgical exploration. The 403 women enrolled between 1990 and 1997 were randomized to receive either 45 Gy external beam radiotherapy at a dose of 1.8 Gy per fraction to the pelvic and periaortic region (with a superior field border at the space between L1 and L2), or the same dose schedule and total dose of external beam radiation to the whole pelvis alone (treatment field extended to the space between L4 and L5) in addition to 2 cycles of fluorouracil 4000 mg/m² over a 96 hour period plus an intravenous infusion of cisplatin 75 mg/m² over a 4 hour period. Three cycles of chemotherapy were scheduled at 3 week intervals. All patients also received low dose rate, intracavitary radiotherapy performed within 2 weeks after completion of the pelvic radiation with the goal of keeping the total duration of treatment under 8 weeks wherever possible. The total cumulative dose to point A was to be at least 85 Gy.

As seen with the clinical trials of chemotherapy in high risk, early stage, cervical cancer patients, there was a significant improvement in the overall survival and the disease free survival in the treatment arm which included chemotherapy, of these women with more advanced cancers.[9] This observation was made despite the fact that patients treated with radiation therapy alone received both pelvic and periaortic radiation whereas those who received chemotherapy with radiation had external beam radiation confined to the whole pelvis. The estimated 5 year survival was 73% for the treatment group who received cisplatin vs. 58% for radiation therapy alone (p=

.004). Likewise, the disease free survival was 67% vs. 40%, respectively (p < .001). The morbidity in both treatment arms was approximately equal. Thus, as with high risk, early stage patients, the addition of chemotherapy with cisplatin and fluorouracil to treatment with external beam and intracavitary radiation significantly improved survival compared to treatment which did not include chemotherapy, among women with locally advanced cervical cancer.[9]

GOG 120, the final cooperative group clinical trial performed in North America relevant to this subject, was carried out simultaneously with the RTOG trial published by Morris et al.[9] and enrolled patients with stages IIB through IVA cervical cancers. This trial was an effort by GOG to demonstrate whether cisplatin based chemotherapy administered with conventional radiotherapy to patients with locally advanced disease would provide a similar survival benefit to that demonstrated with high risk, early stage, cervical cancer patients. A secondary goal of this trial was to determine whether modern chemotherapy treatment strategies should also include the agent hydroxyurea. The rationale for addressing hydroxyurea as a possible agent for inclusion in treatment protocols for this disease relates to early GOG studies of hydroxyurea as a radiation sensitizer for locally advanced disease. The promising results of GOG 4, published in 1979 by Hreshchyshyn et al.[10] for patients with Stages IIIB and IV disease, were the first to demonstrate the importance of chemotherapy and/or a radiation sensitizing agent in the treatment of locally advanced, cervical cancer. Subsequent trials by GOG employing hydroxyurea in the treatment of locally advanced, cervical cancer patients lacked controls treated with radiotherapy alone.[11,12] Thus the precise role of hydroxyurea in the treatment of the disease, while promising, remains unconfirmed in clinical trials. Accordingly, hydroxyurea was integrated into this complex, 3-treatment arm, clinical trial to assess its potential role with and without concomitant chemotherapy and to compare with standard chemotherapy excluding hydroxyurea.

Between 1992 and 1998, GOG enrolled 526 women in this randomized trial of radiotherapy in combination with 3 concurrent chemotherapy

regimens: cisplatin alone, cisplatin combined with fluorouracil plus hydroxyurea, and hydroxyurea alone. Patients with disease outside the pelvis as well as those with either intracavitary or periaortic disease were ineligible. Periaortic assessment was carried out by extraperitoneal, periaortic lymphadenectomy.[13] Radiation therapy was administered to the whole pelvis in either 24 fractions totalling 40.8 Gy or 30 fractions totaling 51.0 Gy, followed 1 - 3 weeks later by intravitreal brachytherapy. The total dose of radiation delivered to point A was 80.8 Gy in patients with stage IIB and 81.0 Gy in patients with higher stage disease. The total dose delivered to Point B was 55.0 Gy in patients with stage IIB disease and 60.0 Gy in patients with more advanced disease. The upper extent of the pelvic field was the upper margin of L5 and the duration of radiotherapy was limited to 10 weeks. Chemotherapy was delivered as one of the following regimens: 1) cisplatin 40 mg/m² of body surface area intravenously 4 hours before radiotherapy on day 1 of weeks one through six, 2) cisplatin 50 mg/m² IV on days 1 and 29 plus fluorouracil 4 g/m² as a 96-hour infusion on days 1 and 29 plus hydroxyurea 2gm/m² orally twice weekly before radiotherapy from weeks one through six, or, 3) hydroxyurea 3 gm/m² orally twice weekly 2 hours before radiotherapy weeks one through six of therapy.

The results of this trial again confirmed the superiority of a platinum based chemotherapy regimen over one which did not include cisplatin. The progression free survival at 24 months was 67% for the treatment arm which contained cisplatin alone and 64% for the treatment arm which included cisplatin, fluorouracil and hydroxyurea, versus 47% for the hydroxyurea arm of the treatment ($p < .001$ for both platinum regimens as compared with hydroxyurea alone). Similarly, the relative mortality risk was .61 for cisplatin alone versus hydroxyurea alone, and .58 for cisplatin plus fluorouracil plus hydroxyurea versus hydroxyurea alone.[14] As demonstrated with the clinical trial published by Morris et al.[9] for RTOG, this GOG trial confirmed that cisplatin-containing chemotherapy regimens, when administered in conjunction with standard radiation therapy, improve the rate of overall survival and progression free survival among women with locally

advanced cervical cancer as compared with women who are not treated with a platinum-containing regimen. Furthermore the data demonstrated that hydroxyurea alone is inferior to a chemotherapy regimen that contains cisplatin with or without hydroxyurea as a radiation sensitizer.

The main role for chemotherapy in the treatment of advanced (Stage IVB) or recurrent, cervical cancer patients is palliation since chemotherapy rarely results in a durable, complete response in these patients. In that regard GOG, in particular, has carried out several clinical trials to define better the role of chemotherapy in the palliation of these patients. GOG 43 was designed to determine whether cisplatin dose intensity, the most active drug for this disease, influenced the response rate in this patient population. Patients randomized to receive cisplatin 50 mg/m² every three weeks had a response rate of 20.7%, whereas those treated with twice this dose at 3-week intervals had a response rate of 31.4%, confirming that response rates were dose dependent. Those women randomized to receive 20 mg/m² for 5 days every 21 days had a 25.0% response rate.[15] GOG 64 addressed the issue of the duration of administration of cisplatin infusions and its impact on response rate. Patients who received rapid infusion of cisplatin 50 mg/m² at 1mg/min were reported to respond the same as those who received a 24 hour cisplatin infusion of the same total dose. In this trial the overall response rate was 18% for both treatment arms although substantially less nausea and vomiting was reported in the 24-hour infusion group.[16] GOG 77 investigated other platinum-containing agents and their possible role in the treatment of patients with advanced or recurrent cervical cancer. The response rate reported in 361 patients eligible for response assessment from this trial was 15% for carboplatin but only 11% for iproplatin.[17] Clearly, these platinum analogs were shown to be inferior to cisplatin as a single agent.

Finally a variety of multi-agent chemotherapy regimens for women with Stage IVB or recurrent cervical cancers were studied in various GOG protocols. GOG 110 studied cisplatin alone vs. cisplatin combined with either mitolactol or ifosfamide with mesna in 438 eligible patients.

The platinum plus ifosfamide arm provided the best measurable response rate of the 3 regimens at 31%, which was a significant improvement over cisplatin alone at 18%.[18] The cisplatin/ifosfamide regimen was administered as cisplatin 50 mg/m² with ifosfamide 5 g/m² as a 24-hour infusion plus mesna 6 g/m² for 12 hours after the ifosfamide infusion every 3 weeks up to 6 courses. GOG 149 was a logical follow-up study to GOG 110 and compared the cisplatin plus ifosfamide as administered in GOG 110 versus the same regimen with the addition of bleomycin. In this trial of 287 evaluable patients, the two treatment arms had virtually identical response rates of 32% (without bleomycin) and 31.2% (bleomycin containing arm), thereby demonstrating that the addition of bleomycin did not add to the therapeutic benefits of the platinum/ifosfamide regimen.[19] Finally, GOG 169 investigated cisplatin alone versus cisplatin in combination with paclitaxel, in 264 evaluable patients. The platinum/paclitaxel arm was superior to cisplatin alone with response rates of 36% versus 19.4%, respectively.[20] Indeed, based upon these various trials it appears that the most active regimens are cisplatin in combination with paclitaxel or ifosfamide. Unfortunately, treatment results remain modest, consistently less than 40%, the duration of response in most instances is only a few months and durable clinical responses continue to be seen infrequently.

CONCLUSION

In summary, there have been major advances in the past 20 years in the treatment both of intermediate and high risk patients with early stage cervical cancer and of poor prognosis patients with locally advanced disease. Specifically, intermediate risk stage IB patients with two or more poor prognostic features of deep stromal infiltration, capillary lymphatic space involvement, and/ or large tumor volume, when treated primarily by surgery, have improved survival when given adjuvant radiotherapy as compared with surgery alone. The role of chemotherapy in this patient population has not been established. On the other hand, high risk, early stage patients (Stages IA2-IB2) with either metastatic disease to the pelvic

lymph nodes, occult parametrial extension, compromised surgical margins or larger tumor volume, when managed primarily by surgery, achieve survival advantage by the addition of pelvic radiotherapy combined with a platinum based chemotherapy regimen, compared to adjuvant radiotherapy alone. Likewise, locally advanced cervical cancer (Stages IIB-IVA) is treated more effectively with better survival demonstrated when radiation therapy is combined with a platinum-containing chemotherapy regimen, compared to radiotherapy alone. Finally, while certain combinations of platinum-based chemotherapy regimens have been demonstrated to provide palliation to approximately one third of the patients with advanced or recurrent cervical cancer, these benefits most frequently are transient and durable responses are only seen rarely. Quality of life and cost issues need to be addressed to determine whether the benefits of palliative chemotherapy are sufficient to justify its continued use in patients with Stage IVB or recurrent cancer of the cervix.

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