The impact of pre-therapy extraperitoneal surgical staging on the evaluation and treatment of patients with locally advanced cervical cancer

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Summary

Objective: The use of extraperitoneal surgical staging prior to treatment in patients with bulky or locally advanced cervical cancer allows the detection and treatment of disease beyond the standard pelvic radiation fields. This study was conducted to evaluate the impact of extraperitoneal surgical staging in the treatment and outcome of patients with locally advanced cervical cancer.

Methods: 51 patients with locally advanced cervical cancer treated between 1985 and 1998 were retrospectively reviewed. Information on morbidity, usefulness, and results of surgery and patterns of disease recurrence were obtained. Survival distributions were calculated by the Kaplan-Meier product limit method and compared with the log-rank test.

Results: All 51 women were surgically staged by an extra-peritoneal approach. Preoperative CT scans (n=27) when compared with surgical findings showed sensitivity for pelvic and para-aortic lymph node metastasis of 39%, specificity of 88%, positive predictive value of 39% and negative predictive value of 88%. Lymph node metastases were found in 30/51 patients (59%). There were no significant treatment delays or surgical morbidity as a result of extra-peritoneal surgical staging. In 21 patients (41%), the highest level of involved nodes was in the pelvis and they were treated with pelvic radiation. The para-aortic nodes were involved in nine patients (18%) and were treated with extended field radiation. All patients also received concurrent radiosensitization with chemotherapy. The estimated survival for the entire group was 60% at 5 years. For node negative patients, estimated 5-year survival was 67% while it was 54% for all node positive patients (p=0.17). Analysis according to anatomic site of involved nodes showed that the estimated 2-year and 5-year survival for those with pelvic nodal involvement was 81% and 64%, respectively. However, in the group of nine patients with para-aortic nodal disease, the estimated 2-year survival was 44%. Five (56%) were dead of disease with a median time to death of 16.0 months and four patients (44%) were alive with a median duration of follow up of 16.1 months. There was a statistically significant difference in survival for the group of patients with positive pelvic nodes only compared to the group with positive para-aortic nodes (p=0.03). The estimated 5-year survival by FIGO stage was 80%, 70% and 51% for stages Ib, II, III, disease, respectively. Factors that did not significantly affect survival included age, histology and type of chemotherapy.

Conclusions: Pre-therapy extra-peritoneal surgical staging resulted in treatment modification in 18% of patients with locally advanced cervical cancer. The morbidity from surgery and subsequent radiation therapy was acceptable. The procedure is recommended to allow for individualization of treatment in patients with local-regional cervical cancer.

Key words: Extraperitoneal; Surgical staging; Cervical cancer; Extended field radiation; Para-aortic nodes.

Introduction and Background

Cervical cancer is a major public health problem. Each year, the World Health Organization estimates about 465,000 new cases and in excess of 200,000 deaths from the disease [1]. Although accurate knowledge of the extent of disease is a prerequisite for the effective control of any malignancy, in cervical cancer the definition of the extent of disease traditionally comes from clinical staging and non-invasive diagnostic tests. Unfortunately, clinical staging is notoriously inaccurate with only a 52%-60% correlation between the clinical stage and subsequent surgical stage [2, 3]. The most likely foci of occult metastatic disease are the pelvic and paraaortic lymph nodes, and there is substantial evidence to show that patients with lymph node metastasis have lower overall survival, disease-free survival, and survival after recurrence [4, 5]. Indeed, in locally advanced cercical cancer (FIGO stages IIB-IVA), the para-aortic nodes will be involved in 5%, 12-16%, 25-33%, and 12-100% of stages 1b, II, III, and IV, respectively [6].

The use of extraperitoneal surgical staging prior to treatment in patients with bulky or locally advanced cervical cancer is a controversial but theoretically appealing concept since it will permit individualization of therapy based on specific patterns of disease spread. The question is whether or not the identification and aggressive primary treatment of lymph nodes results in improved overall survival that is not overshadowed by an increase in morbidity and mortality. There is now evidence to suggest that despite conveying an ominous prognosis, as many as 25-30% of patients with histologically proven para-aortic nodal disease may be salvaged by extended-field irradiation [7, 8]. In fact, more recent studies have shown that extended-field irradiation, as well as the use of concomitant chemotherapy improves local control and

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overall survival [9-12]. However, current imaging modalities are unlikely to help in selecting patients likely to benefit from such therapy as they have significant limitations in detecting para-aortic nodal metastasis [13].

Surgical staging leads to the ability to detect and treat metastatic disease beyond the standard pelvic radiation treatment fields. Although elective irradiation of the para-aortic lymph nodes might improve the outcome of treatment for patients with loco-regional cervical cancer, the results of two randomized controlled trials are conflicting. The Radiation Therapy Oncology Group (RTOG) found a significant increase in survival among patients randomly assigned to receive para-aortic irradiation [14]. On the other hand, the European Organization for Research and Treatment of Cancer (EORTC) found no significant difference in survival or metastasis rate between the two treatment arms [15]. Since the role of this elective, potentially morbid treatment of the para-aortic lymph nodes remains uncertain, it will be important to select patients at higher risk, who may truly benefit from such treatment. Some investigators advocate routine surgical staging in all women with locally advanced disease, and suggest that there may even be a therapeutic benefit to debulking nodes that might be otherwise difficult to treat with conventional radiation doses [16-18].

The extra-peritoneal approach for surgical staging of cervical cancer was first described over 20 years ago [19]. Theoretically, the approach should be associated with significantly less risk of adherent, fixed bowel loops postoperatively, and hence decreased morbidity from both pelvic and extended field radiation therapy. In our institution we have adopted this approach for over two decades. Further, we have practiced radiation sensitization with concomitant chemotherapy during the same time period. The goals of the present study were to evaluate the impact of extra-peritoneal surgical staging in the treatment and outcome of patients with locally advanced cervical cancer. Specifically, we report on morbidity, usefulness, and results of surgery and patterns of disease recurrence.

Materials and Methods

The record of 51 patients with locally advanced cervical cancer who were surgically staged at the Roswell Park Cancer Institute between January 1985 and December 1998 were retrospectively reviewed. During this time period, a total of 294 patients with locoregional cervical cancer (bulky stage 1B, IIB, III and IVA) were treated. The review included out-patient and in-patient treatment, radiation doses and fields, as well as treatment complications. The pre-treatment work-up consisted of a complete history and physical examination, cervical biopsy, chest radiography, computed tomographic scan of the abdomen and pelvis, and complete hematologic, renal, and liver function studies.

The surgical technique consisted of unilateral or bilateral J-incisions. The external oblique, internal oblique and trasversus abdominis muscles are incised with electrocautery. The dissection is carried down to the abdominal peritoneal envelope, which is separated from the abdominal wall. Clinically suspicious pelvic lymph nodes, as well as para-aortic nodes extending from the aortic bifurcation to the third portion of duodenum, were excised. Patients underwent removal of pelvic nodes followed by removal of common iliac and para-aortic nodes.

Pelvic teletherapy consisted of 45-60 Gy delivered in 1.8 Gy fractions using either a 6 MeV or 25 MeV linear accelerator, depending on the anterior-posterior separation of the individual. Shaped pelvic fields were used with the superior border at the S1L5 junction, extending inferiorly to the obturator foramen, and laterally to the bony pelvis with a 1 to 2 cm margin.

For patients with positive common iliac or para-aortic nodes, the usual pelvic radiation fileds was extended to the level of the 10th thoracic vertebra. The width of this extended portal is sufficient to encompass the lateral extent of the transverse processes of the vertebral bodies, and is usually 8 cm in diameter. These patients received 4500-5000 rads of external radiation to the extended field over five weeks, through parallel-opposed anterior-posterior, posterior-anterior, and lateral portals. One or two brachytherapy applications using cesium-137 were then used to deliver an additional 30-40 Gy to point A. When chemotherapy was administered as radiation sensitizer, hydroxyurea was administered concomitantly with radiation at a dose of 80 mg/kg every third day and continued for 12 weeks. In instances where cis-platinum was administered, the dose was 1mg/kg per week. All treatment related complications were recorded. Complications were considered minor if the patient had symptoms requiring no significant intervention.

Survival distributions were calculated by the Kaplan-Meier product limit method [20] and tests of significance with respect to survival distributions were based on the log-rank test [21]. Cox's proportional hazards model was used for the multivariate analysis [21].

Results

The median age of the 51 surgically staged patients was 44 years (range 26-67). Stage distributions were as follows: five (9.8%) women had bulky stage 1B disease, 16 (31.4%) were stage IIB, two (3.9%) were stage IIIA, 25 (49%) were stage IIIB, two (3.9%) were stage IVA, and one (2%) was stage IVB. Tumor histology was squamous in 39 patients (76%), adenocarcinoma in eight patients (16%), adenosquamous in three patients (5.9%) and neuroendocrine in one patient (2%) (Table 1).

Surgical staging was accomplished by the extra-peritoneal technique in all cases. The median number of para-aortic lymph nodes removed was six (range 1-13). The median number of days to initiate radiation therapy was 14 (range 7-21). Surgical complications occurred in 13 women and included febrile morbidity (3), pelvic abscess (1), pelvic lymphocyst (2), wound infection (4), wound breakdown (1), and deep venous thrombosis (1). No complication resulted in permanent injury.

Lymph node metastasis was found in 30 of the patients (58.8%). In 21 patients, (41.2%) patients, the highest level of involved nodes was in the pelvis. The para-aortic nodes were involved in nine patients (17.6%) of which one was stage 1B, seven were stage IIIB and one was stage IVA. The characteristics of these patients are presented in Table 2. Preoperative CT scans were performed in 27 cases, including five of the patients with para-aortic nodal metastases. CT scan correctly identified para-aortic nodal metastases in two of these patients. The

Table 1. — *Patient characteristics*

Characteristics	
Evaluable patients	51
Age (median/range)	44 (26-27)
FIGO stage	
1B	5 (9.8%)
IIB	16 (31.4%)
IIIA	2 (3.9%)
IIIB	25 (49%)
IVA	2 (3.9%)
Histology	
Squamous cell carcinoma	39 (76%)
Adenocarcinoma	8 (16%)
Adenosquamous	3 (5.9%)
Small cell (neuroendocrine)	1 (2.0%)
Nodal status	
Nodal negative	21 (41.2%)
Positive pelvic nodes	21 (41.2%)
Positive para-aortic nodes	9 (17.6%)
Recurrences	
Local/pelvic	14
Pelvic/distant	5
Distant	8
Patient status/survival	
Dead of disease	
Dead of intercurrent disease	
Alive with disease	
Alive with no evidence of disease	

overall sensitivity of CT scan for pelvic and para-aortic lymph node metastasis was 39%, specificity was 88%, positive predictive value was 39% and negative predictive value was 88%.

All patients were treated with pelvic radiation therapy. In addition, eight patients with para-aortic nodal disease-received extended field radiation. One patient with para-aortic nodal metastasis was subsequently found to have biopsy proven metastasis to the scalenae nodes and was treated with palliative pelvic radiation therapy. All other patients were treated with curative intent. The mean radiation dose to point A was 8607 cGy and to point B was 6270 cGy. Chemotherapy was administered to 49 patients as a radiation sensitizer. Thirty-seven patients received hydroxyurea. The remaining patients received cis-platinum either alone (8 cases) or in combination with 5FU dosed at 1000 mg/m^2 continuous infusion days 1-4, days 28-32 (1 case) or ifosfamide (2g, days 1-3). The median duration of radiation therapy was 43.0 days.

Analysis of survival by nodal status showed that of the 20 node-negative women treated with a curative intent, six (30%) patients died with a median time to death of 20.3 months; 14 patients (70%) were alive after a median follow-up of 90.2 months. Of the latter group, eight (57.1%) patients were alive without evidence of disease. In the case of the 21 patients with positive pelvic nodes, nine (43%) were dead of disease with a median time to death of 25.6 months; 12 (57.1%) were alive after a median follow-up of 93.1 months. Of these, six (50%) were alive without evidence of disease. Finally, in the group of nine patients with para-aortic nodal disease, five (56%) were dead of disease with a median time to death of 16.1 months; four patients (44%) were alive with a median duration of follow-up of 16.1 months. There was a significant difference in survival in the group of patients with positive pelvic nodes only compared with the group with positive para-aortic nodes (p=0.03).

Kaplan-Meier survival curves evaluating survival are shown in Figures 1 to 3. The estimated survival for the entire group was 60% at five years. For node-negative patients, estimated 5-year survival was 67% while it was 54% for node positive patients (p=0.17) (Fig. 1). Survival according to anatomic site of involved nodes is shown in Figure 2. The estimated 2-year and 5-year survival for those with pelvic nodal involvement were was

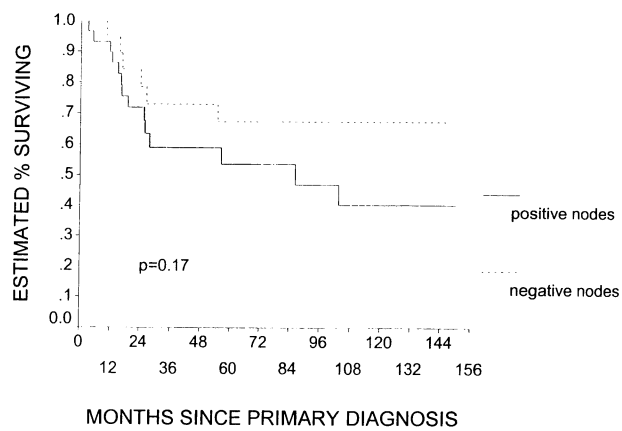

Figure 1. — Survival by nodal status.

Table 2. — *Characteristics of patients with para-aortic nodal metastasis*

No.	Stage	Histology	Chemotherapy	PFI	Site of recurrence	Second treatment	Status
1	IIIB	Adenocarcinoma	Cis/Ifos	0 mos.	Pelvis/distant	Interferon/Adriamycin	DOD 5 mos.
2	IIIB	SCC	Cis/Ifos	16 mos.	Distant	Interferon/Adriamycin	DOD 16 mos.
3	IIIB	Small cell	Hydroxyurea	9 mos.	Pelvis/distant	Cis/Ifos/Bleomycin	DOD 15 mos.
4	IVA	Adenosquamous	Carbo/Taxol	5 mos.	Distant	Irinotecan	AWD, 14 mos.
5	IIB	SCC	Cis	20 mos.	None	None	DWD, 20 mos.*
6	IIIB	SCC	Cis	5 mos.	Distant	None	DOD, 9 mos.
7	IIIB	SCC	Cis	18 mos.	None	None	NED, 18 mos.
8	IB	SCC	Cis	13 mos.	None	None	NED, 13 mos.
9	IIIB	SCC	Hydroxyurea	15 mos.	Pelvis	Cisplatinum/Taxol	DOD, 277 mos.

DOD = dead of disease; DWD = dead without disease; AWD = alive with disease; NED = no evidence of disease; CIS = Cisplatinum; Ifos = ifosfamide; SCC = squamous cell carcinoma; * = Died of pulmonary embolism.

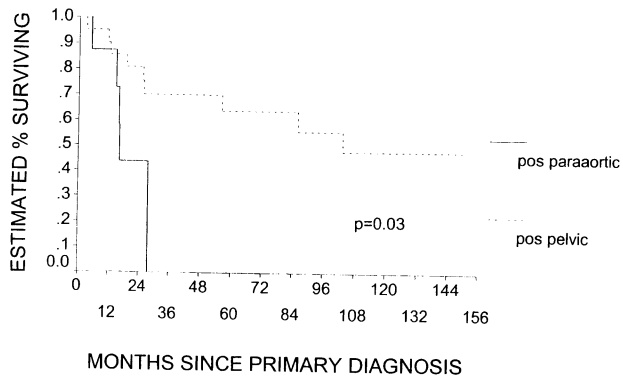

Figure 2. — Survival by location of nodal involvement.

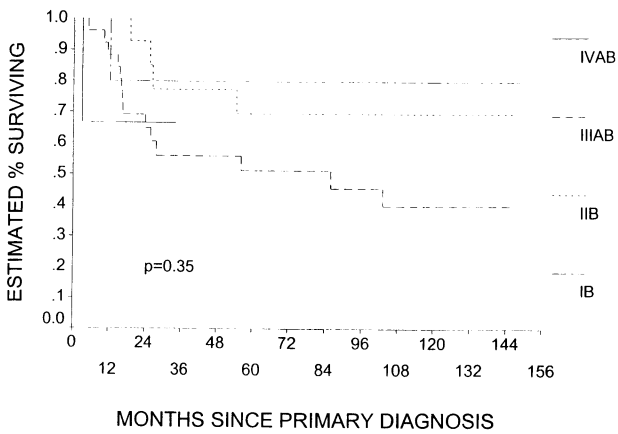

Figure 3. — Survival by FIGO stage.

81% and 64% respectively. By contrast, for patients with para-aortic nodal involvement, the estimated 2-year and 5-year survivals were 44% and 0%. This difference was statistically significant (p=0.03). Survival by FIGO stage (Figure 3) showed estimated 5-year survival of 80%, 70%, and 51%, for stages Ib, II and III disease, respectively.

Overall, 27 patients (52.9%) developed recurrent disease during the follow-up period. This consisted of nine node-negative patients (33.3%), 14 patients with pelvic nodal metastasis (51.9%) and four patiens with para-aortic nodal disease (14.8%). The presence of lymph node metastasis was a significant factor in recurrence (p=0.002). Analysis of the sites of recurrence showed that 14 patients had pelvic recurrence only (6 node-negative patients, 7 patients with pelvic nodal metastasis and 1 patient with para-aortic disease). Five patients had pelvic and distant recurrence (1 node negative patient, 3 patients with pelvic nodal metastasis and 1 patient with para-aortic disease). Eight patients had distant recurrence alone (2 node negative patients, 4 patients with pelvic nodal metastasis and 1 patient with para-aortic disease). There was no significant relationship between lymph node status and site of recurrence (p=0.699). Four patients in the study had progressive disease at completion of treatment. Two patients in this group had para-aortic nodal disease and were dead at five and 16 months, respectively. The remaining two patients had no evidence of pelvic or para-aortic nodal disease and died at three and 18 months.

Twenty-five patients (49%) experienced no complications from radiation therapy. Another four patients (7.8%) had complications requiring surgical intervention [recto-vaginal fistula (2), vaginal necrosis (1), small bowel obstruction (1)]. The remaining patients experienced minor complications such as radiation enterocolitis, and cystitis, which were managed medically.

Multivariate analysis of prognostic factors showed that the presence of para-aortic nodal metastasis was the most adverse prognostic factor for survival. Age, histology and type of chemotherapy did not significantly affect survival.

Discussion

Cervical cancer is traditionally managed as if it were a disease confined to the pelvis. In a series of surgical staging studies for cervical cancer, the Gynecologic Oncology Group (GOG) identified para-aortic nodal metastases in 5%, 21% and 31% of stages 1B, IIB and IIIB, respectively [22, 23]. The most important value of information from surgical staging is that it allows accurate individualization of treatment. If disease is limited entirely to the pelvis, the patient can be treated confidently using standard pelvic treatment methods. However, when the para-aortic nodes are involved, the radiation field can be extended to include the para-aortic area. Although Morris *et al.* [24] found that the combination of pelvic radiation and concomitant chemotherapy with cisplatin and fluorouracil was more effective for locally advanced cervical cancer than pelvic and prophylactic para-aortic radiation alone, the authors concluded that selected patients with known metastases to the para lymph nodes may still benefit from para-aortic radiation. At issue is whether or not the information obtained from surgical staging could be obtained from less invasive imaging studies, immediate and late sequelae of the procedure, the efficacy of extended field irradiation in node positive patients, and the impact on progression-free interval and overall survival.

Several imaging modalities such as lymphangiography (LAG), CT, MRI and PET scan have been evaluated in cervical cancer for detecting para-aortic nodal metastasis. The sensitivies of CT, LAG, MRI and PET are 79%, 34%, 55% and 75%, respectively; and the speficifities are 73%, 96%, 71% and 92% [23, 25, 26]. The overall positive predictive values (PPV) are 48% for LAG, 73% for CT, 59% for MRI and 75% for PET; while white the overall negative predictive values (NPV) are 82%, 92%, 68% and 92%, respectively, for LAG, CT, MRI and PET [23, 25, 26]. Although only 27 patients had CT evaluation in our study, the sensitivity, specificity, PPV and NPV of 39%, 88%, 39% and 88%, respectively, are somewhat lower than in previously reported studies. Since there are significant limitations with these modalities, surgical staging remains the best method for asses-

sing nodal involvement to allow identification of patients who are at high risk for distant failure. The control and prevention of distant metastasis is especially important, since local control can now be achieved in over 60-75% of women with stage II and III disease [9, 10, 27].

The nine patients (18%) identified in our study with para-aortic nodal disease received extended field radiation, as well as concomitant chemotherapy. Berman *et al.* [22] reporting a Gynecologic Oncology Group experience with staging laparotomy also indicated that 20% of 436 patients (Stages IIB through IVA) had para-aortic nodal metastasis. Thus, for almost one in five woment with locally advanced cervical cancer, a modification of the standard pelvic radiation field was necessary because of the information obtained from surgical staging. Although 44% of patients with para-aortic nodal disease were alive with a median duration of follow-up of 16.1 months, this was significantly less than in the group of patients with positive pelvic nodes only where 57.1% were alive after a median follow-up of 93.1 months. There were also significant differences in the estimated 2 and 5-year survivals in the two groups. Thus, para-aortic nodal disease confers a worse prognosis and this data underlines the need to identify this subgroup of patients for more aggressive therapy. It is likely that the survival rates for the group with para-aortic nodal disease could have been worse without the individualization of therapy which surgical staging allowed.

The results by other authors [16, 17, 28, 29] are even more encouraging. Goff *et al.* [28] found no difference in survival between those women with pelvic vs. para-aortic nodal disease and reported an estimated 5-year survival for patients with para-aortic nodal metastasis of 52%. Cosin *et al.* [16] reported 5-year survival of 43% for patients with macroscopic para-aortic nodal involvement. In the analysis by Kim *et al.* [17], the 5-year survival for patients with para-aortic nodal metastasis with complete nodal resection was 35%. Finally, data from GOG 125 [29] evaluating patients with para-aortic nodal metastasis who were treated with extended field radiation and concurrent 5FU/cisplatin showed overall survival of 39%. All of these studies, as well as our study, demonstrate an improvement in survival when compared with previously reported cure rates of 22% in patients with documented para-aortic nodal metastasis.

Another theoretic advantage of surgical staging is the therapeutic benefit of debulking large lymph nodes that are beyond the ability of standard radiotherapy to sterilize. Although this issue can only be adequately addressed in a randomized control fashion, the medium-term survival of patients in our study as well as other studies [16, 17, 29] provides indirect evidence of benefit. Further, in a study by Hacker *et al.* [18], the actuarial 5-year survival for a group of eight patients with bulky para-aortic nodal disease was 48%. By contrast, Jolles *et al.* [30] reported on 42 women with cervical cancer and positive pelvic/para-aortic lymph node metastasis on the basis of positive lymphangiograms, treated with extended field radiation. The five-year disease-free survival was only 22%. Piver *et al.* [31] prospectively studied nine consecutive patients with extensive para-aortic lymph node metastasis that were treated with pelvic radiation with concomitant weekly cis-platinum, followed by monthly cis-platinum based combination chemotherapy. Only 22% of the patients were alive with no evidence of disease, 56% were dead of disease and 22% were alive with disease after a follow-up of 12-24 months. Fletcher [32] has estimated that a radiation dose of 50 Gy would sterilize over 90% of microscopic nodal metastases, but not more than 50% of grossly positive nodes. Further, since doses as high as 60 Gy are required to control disease measuring 1-2 cm, removal of enlarged lymph nodes may allow treatment with lower doses of radiation to control disease while minimizing complications.

There was no significant surgical morbidity in our study, and none of the patients experienced significant treatment delays as a result of surgery. The impact of pre-therapy surgical staging on radiation morbidity has previously been reported from our institution [33]. In that report, only nine (14%) of 66 patients with radiation complications requiring surgical repair or causing death had undergone pre-therapy surgical staging via an extra-peritoneal approach, compared with 57 patients (86%) that were evaluated via a transperitoneal incision ($p<0.0001$). In the present report there was no treatment related death and radiation morbidity requiring surgical repair occurred in only 7.8% of the patients. Other groups have evaluated the morbidity associated with radiation therapy following pre-therapy surgical staging [3, 19, 34]. In the study by Berman *et al.* [19], using an extra peritoneal staging technique, the complication rate secondary to radiation induced bowel injury declined from 30% to 2.5%. This most likely reflects the lack of intra-peritoneal bowel adhesions with the extra-peritoneal staging approach. Chen *et al.* [35] recently evaluated adhesion formation in a porcine model comparing laparoscopy to laparotomy – both extra and transperitoneal approaches. Transperitoneal laparotomy was associated with a 100% adhesion rate with a mean adhesion score of 6, compared to an adhesion rate and mean adhesion score of 30% and 0.4 with laparoscopy, and 20% and 0.7 for extra-peritoneal laparotomy, respectively.

Although our results are less favorable than those reported by other authors [[16, 17, 28, 29], we conclude that not all cervical cancer patients with involved para-aortic lymph nodes are destined to die, at least in the medium term. Since these patients are at high risk for eventual distant metastases, para-aortic radiation for patients with involved lymph nodes is of benefit if distant metastasis are absent and loco-regional control is safely achieved both in the pelvis and para-aortic region. Recent studies have demonstrated significant improvement in survival for women with locally advanced cancer who receive radiation and concurrent chemotherapy [10, 11, 12]. The goal of management in patients with locally advanced cervical cancer will be to identify patients at high risk for para-aortic nodal spread using the extra-peritoneal approach for staging. Patients who also have a good chance of obtaining local control, and who are medically fit to undergo extended field radiation therapy

should be so treated, thus justifying the added costs and potential morbidity of additional staging beyond that which is recommended by FIGO. Future randomized controlled studies are warranted to assess the impact of pre-therapy surgical staging performed laparoscopically or via the extra-peritoneal approach on disease-free and overall survival.

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