Short duration neoadjuvant chemotherapy followed by radiotherapy for advanced carcinoma of the cervix: results and prognostic variables

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Summary

Purpose: The value of neoadjuvant chemotherapy in squamous cell carcinomas of the cervix has not been proven. It has been suggested that the potential benefit of this therapy on local and occult metastatic disease could be offset by delaying effective radiation therapy and selection of more aggressive tumor clones. This report examines the potential impact of short duration neoadjuvant chemotherapy on the response and outcome of advanced carcinoma of the cervix.

Materials and Methods: Between 1993 and 1997, 37 patients with advanced squamous cell carcinoma of the cervix (FIGO Stages IIB to IV) were enrolled in a prospective nonrandomized study using short duration neoadjuvant chemotherapy. Median age was 57 years (range: 34-70). Twenty-one patients (57%) had Stage IIB disease, one (3%) had Stage IIIA, 11 (30%) Stage IIIB, and four (11%) had Stage IV disease. The average tumor diameter at presentation assessed by physical examination and by CT scan measurements was 5.3 + 1.9 cm and 5.3 + 1.4 cm, respectively. Patients received three cycles of chemotherapy consisting of cisplatin 50 mg/m^2 and vincristine 1 mg/m^2 for 1 dose and bleomycin 25 mg/m^2 daily for three days. Cycles were repeated every ten days. All patients started definitive radiotherapy within a week from the end of chemotherapy. Radiation therapy consisted of whole pelvis radiotherapy followed by 1-3 sessions of low dose rate brachytherapy.

Results: Response to neoadjuvant chemotherapy was as follows: seven patients (19%) had minor or no response, one patient had progressive disease, and 28 (76%) had more than 50% tumor reduction; 14 of them (38%) had no clinical evidence of residual tumor. Chemotherapy was discontinued in one patient after the second cycle because of significant changes in pulmonary function tests (PFT), and one patient developed a grade 4 urinary complication after radiotherapy. Median follow-up time for the whole group was 24 months (range: 1-67). Five-year actuarial rates of local control and disease-free survival were 47 and 42%, respectively. At three years, 20 patients (54%) were alive or had died without evidence of disease, and 17 (46%) had succumbed to their disease, with a median time to recurrence of 25 months. Stage and response to neoadjuvant chemotherapy had significant impact on survival, while age, tumor size, and menopausal status did not influence survival.

Conclusions: Our data indicate that short duration chemotherapy followed by definitive radiotherapy is well tolerated and feasible. However, despite a high rate of objective response (76%), and improved survival for responders, there was no obvious long-term survival benefit for the entire group.

Key words: Cervical cancer; Neoadjuvant chemotherapy; Radiotherapy.

Introduction

In many developing countries, including Lebanon, cervical cancer remains a major public health problem with high overall incidence and higher frequency of advanced stage at diagnosis. In a review of uterine tumors registered between 1983 and 1998 at the American University of Beirut Medical Center tumor registry, 569 new patients presented with cancer of the uterine cervix compared to 233 patients with endometrial cancer. Nearly three out of four patients with cervical cancer presented with an advanced stage (Stages IIB to IV) [41]. In contrast, cervical cancer represents only the third most common gynecologic malignancy in the USA [20] where the incidence of cervical cancer is continuously decreasing. However, despite this favorable epidemiologic phenomenon, the overall survival of patients with cervical cancer has idled over the past two decades, after significant advances were introduced by the implementation of modern external and intracavitary radiotherapy techniques [9, 16, 23, 31]. While early stages (≤ IB) respond well to either radical surgery or radiation, locally advanced and bulky tumors still have a recurrence rate over 40% after radical radiotherapy alone.

A number of strategies integrating chemotherapy with local treatment are available, including neoadjuvant chemotherapy before surgical or radiation therapy, radiosensitizing chemotherapy given concurrently with radiotherapy, or postoperative chemotherapy for high risk patients. Sardi *et al.* in a pilot study, reported a high response rate of cervix cancer to neoadjuvant combination chemotherapy including *cis*-platinum, vincristine, and bleomycin [37]. In a later study, they showed that the response to neodajuvant chemotherapy was strongly correlated with the initial tumor volume [39]. Other studies have also demonstrated that cervical cancer is a chemo-

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responsive disease especially with *cis*-platinum- and bleomycin-containing regimens [11, 18, 24, 36, 42]. However, none of these studies or others were able to demonstrate a treatment advantage of combined sequential chemotherapy and radiotherapy over radiotherapy alone [6, 7, 19, 21, 43, 44, 45]. It has been suggested that the potential benefit of neoadjuvant chemotherapy in squamous cell carcinomas on local and occult metastatic disease is offset by delaying effective radiation therapy and selection of more aggressive tumor clones with a higher ability for accelerated repopulation during a conventional course of radiotherapy [4, 29]. Therefore, compressing the duration of neoadjuvant chemotherapy may, in theory, reduce this negative effect while maintaining the potential locoregional and systemic benefits. In this study we examine the feasibility of a short duration, four-week course of neoadjuvant chemotherapy followed by definitive conventional radiation therapy, and its impact on the response rate, treatment outcome, and prognostic determinants of locally advanced cervical cancer.

Materials and Methods

All patients presenting to the American University of Beirut-Medical Center, with advanced squamous cell carcinoma of the cervix Stage IIB to IV, 70 years of age or less, and with no baseline lung disease were enrolled in a prospective nonrandomized study using neoadjuvant radiation therapy followed by definitive radiation therapy. Between September 1993 and November 1997, a total of 37 patients were included in the study. Disease was staged using the FIGO staging system. All patients were required to have a Gynecology Oncology Group performance status of 0-3. The median age was 57 years (range: 34-70). The median gravidity and parity were eight (range:0-15) and six (range: 0-15), respectively; 60% of patients were postmenopausal. Twenty-one patients (57%) had Stage IIB disease, one (3%) had Stage IIIA, 11 (30%) Stage IIIB, and four patients (11%) had Stage IV disease. Seven patients had prior abdominal hysterectomy, four of which were supracervical hyserectomies performed for unclear reasons. Tumor size was assessed by two different examiners prior to and following each cycle of chemotherapy. Initial work-up included complete blood and platelet counts, creatinine, liver function tests, and pulmonary function tests (PFT) including blood gases and spirometry. Computerized tomography (CT) scanning of the abdomen and pelvis were performed as part of the initial work-up and following the last cycle of chemotherapy. Chemotherapy consisted of three cycles of PVB (cisplatin 50 mg/m^2, day 1, vincristine 1 mg/m^2, day 1, and bleomycin 25 mg/m^2, days 1-3) administered ten days apart. All patients had conventional radiotherapy starting one week following the last cycle of chemotherapy. The average time to start radiation from the time of initiating chemotherapy was five weeks. Radiation therapy consisted of external beam radiotherapy to the whole pelvis followed by low-dose rate brachytherapy for 1-3 applications with or without additional parametrial boosts. The median dose of external beam radiation was 55 Gy (range: 38-74) delivered using a 4-field technique with Cobalt 60 photons, at 2 Gy per fraction. The first low-dose rate brachytherapy application was inserted on average seven days after completion of pelvic radiation. The Fletcher-Suit-Delclos tandem and ovoids afterloading system was used with Cesium 137 radioactive sources. The average dose to point A was 38.3 Gy (range: 24.5-64.8). The average total mgRa equivalent was 4616 (range: 1416-9200). The median combined radiation dose to point A (external and intracavitary) was 76.7 Gy (range: 49.45-106.6).

Patients were followed by repeat pelvic examinations, pap smears and radiographic imaging as needed every three months for the first two years and every six months thereafter. Clinical partial response was defined as a decrease in tumor size by more than 50% while complete response was defined as no evidence of tumor by either examination or CT scan imaging. No clinical response was defined as a decrease of less than 50% or no change in tumor size. The primary endpoints were response to chemotherapy and survival. Time to relapse was defined from the date of entry into the study to the date of recurrence. Patients with progressive disease were censored for relapse at the end of radiation therapy, which was approximately two months and half from the date of entry. Disease-free survival was defined as alive with no evidence of disease at the time of last follow-up or death without evidence of disease. Patients lost to follow-up were considered with relapse and censored at the time of their last follow-up visit. Survival was calculated from the date of entry to the date of death or last follow-up. Median follow-up was 26.4 months (range: 2-55). Cumulative survival rates were estimated by the Kaplan-Meier method and compared using the log-rank test. Chi-square and the Student's *t*-test were used for comparative analyses. Statistical significance was defined as $p < 0.05$. Data were analyzed using a SPSS program version 6.0.

Results

Tumor size measured by manual examination at presentation correlated well with measurements taken on CT scan slices. The average tumor diameter was 5.3 ± 1.9 cm (median 5 cm) and 5.3 ± 1.4 cm (median 5.3 cm) for both methods, respectively. Tumor size, evaluated clinically, decreased by 26.1 ± 24.5 %, 56.1 ± 29.8 %, and 71.7 ± 34.2 % following the 1st, 2nd, and 3rd chemotherapy cycle respectively. Table 1 shows the overall response to chemotherapy. Eight patients (22%) had no response: one patient had rapidly progressive disease following the first cycle and died shortly thereafter, two patients (5 %) had no change in size, while five (13%) had less than 50% decrease in size of the tumor. Twenty-eight patients (76%) had more than 50% reduction in tumor measurements including 14 patients (38%) who achieved complete clinical response. One patient discontinued chemotherapy because of pulmonary toxicity. All others received all three scheduled courses with no significant toxicity. Two patients of the group who had complete cli-

Table 1. — *Tumor response to neoadjuvant chemotherapy in carcinoma of the cervix. One patient discontinued chemotherapy because of bleomycin-related lung toxicity.*

Type of response	n	%
Complete	14	38
Partial	14	38
None	7	19
Progressive disease	1	2.5
Treatment interruption	1	2.5
Total	37	100

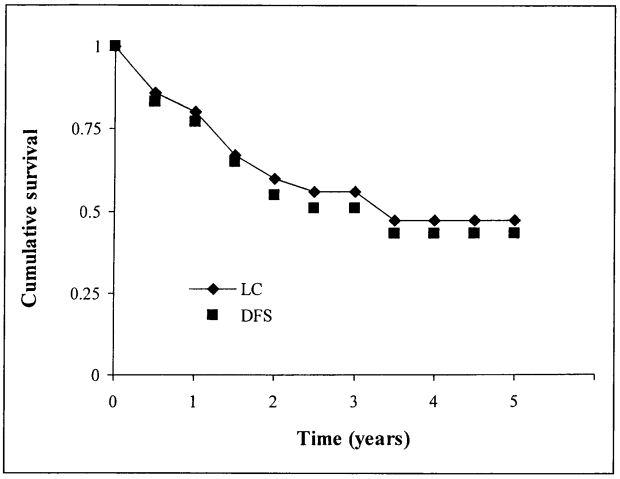

Figure 1. — Actuarial plots of local control (LC) and disease-free survival (DFS).

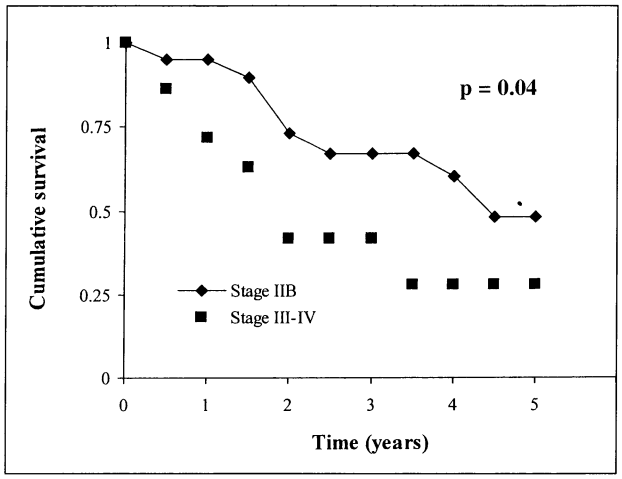

Figure 2. — Cumulative survival as a function of disease stage.

nical response failed to show up for radiotherapy and both returned, at six months and at three years respectively, with extensive recurrence and died shortly thereafter. Radiotherapy was also relatively well tolerated. Two patients complained of hemorrhagic cystitis and/or proctitis, and one patient with Stage IV disease developed vesico-vaginal and recto-vaginal fistulae but remained free-of-disease at three-year-follow-up.

Twenty patients (54%) were alive or died without disease after a median follow-up of 24 months (range: 1-67), while 17 (46%) died of their disease. Thirteen patients recurred after at least a 6-month disease-free interval, with a median time to recurrence of 25 months (range: 1-36). Nine patients recurred loco-regionally, one distantly, and three both loco-regionally and distantly. The 5-year actuarial rates for local control and disease-free survival were 47% and 42%, respectively (Figure 1).

Various potential prognostic factors were examined for their influence on response rate and survival. Table 2 shows the impact of different parameters on response to chemotherapy. Age, menopausal status, gravidity and parity had no impact on the response to induction chemotherapy. There was a non-significant trend for a higher response rate for patients with Stage IIB disease compared to patients with more advanced stages. When examined by tumor size, response of patients with smaller tumors tended to be better than larger tumors but the difference was not significant.

Table 3 shows the relationship between stage and cumulative survival. Patients with Stage IIB survived significantly longer than those with Stages III-IV (median survival 52 months vs 24 months; p = 0.04; Table 4, Figure 2). Also, patients with smaller lesions (< 4 cm) had a better median survival than those with larger lesions (52 *vs* 30 months). However, this was mainly due to an early survival advantage that was lost with longer follow-up, and the overall difference did not reach statistical significance (p = 0.3; Figure 3). Table 4 also shows the impact of response to chemotherapy on overall survival. There was a significant difference in cumulative survival among responders compared to non-responders (54% *vs* 18%; p = 0.003; Figure 4).

Table 2. — *Influence of different patient and tumor variables on the response to neoadjuvant chemotherapy.*

Variable	Whole group	CR/PR	NR/PD	p
Age (median)	57	57	51	NS
Tumor size (median)	5.3	5	5.5	NS
Stage IIB	21 (57%)	68%	32%	NS
Stage III-IV	16 (43%)	33%	67%	
Premenopause	15 (40%)	36%	50%	NS
Gravidity (median)	8	8	7	NS
Parity (median)	6	6	6	NS

NS = not significant;
CR = complete response; PR = Partial response; NR = No Response; PD = progressive disease.

Table 3. — *Influence of disease stage on outcome after neo-adjuvant chemotherapy and radiotherapy for carcinoma of the cervix.*

Stage	NED	Failed	Total
IIB	13 (62%)	8 (38%)	21
IIIA	1		1
IIIB	5 (45%)	6 (55%)	11
IV	1	3	4
Total	20 (54%)	17 (46%)	37

NED = no evidence of disease at last follow-up.

Table 4. — *Cumulative survival as a function of stage and response to chemotherapy; p values were calculated using the log-rank test.*

Variable	n	Survival	p
Stage			
IIB	21	48%	0.04
IIIA-IV	16	28%	
Response to Chemotherapy			
Yes	28	54%	0.003
No	8*	19%	

* 1 patient discontinued chemotherapy because of lung toxicty.

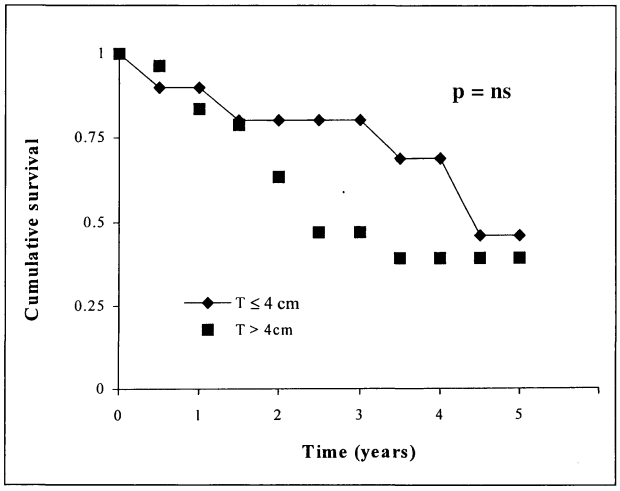

Figure 3. — Cumulative survival as a function of tumor size.

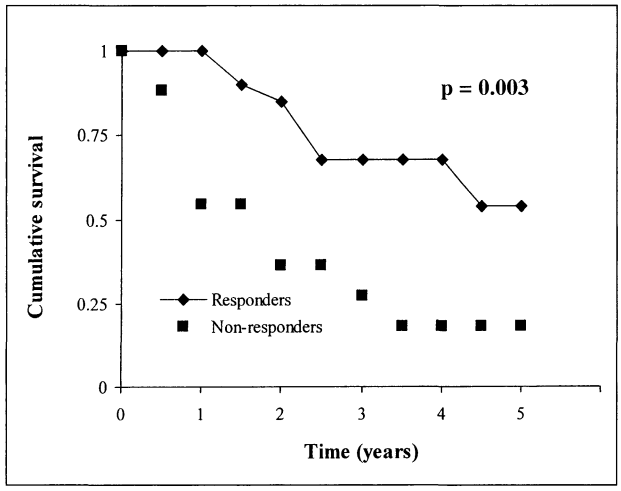

Figure 4. — Influence of objective response to neoadjuvant chemotherapy on survival; p value obtained using the log-rank test.

Discussion

In this study three out of four patients with cervical cancer who received an intensive course of neoadjuvant chemotherapy responded favorably with 38% of them achieving a complete clinical response. Stage and response to chemotherapy had a significant impact on survival. Although responders to neoadjuvant chemotherapy fared better than non-responders, there was no obvious survival benefit for the whole group when compared to published figures. Overall, 54% of the patients were disease-free at last follow-up after an average follow-up of 36 months. This is similar to known survival rates of patients with locally advanced cervical cancer treated by radiation therapy with or without neoadjuvant chemotherapy [9, 16, 23, 31, 42].

The rationale for using adjunctive chemotherapy in cervical cancer is the notion that large tumors are less responsive to radiotherapy due to size, hypoxia and necrosis. Hypoxia decreases cell radiosensitivity by decreasing the number of free oxygen radicals, altering cell cycle distribution, and stimulating the production of cytokines [8, 12, 47]. Chemotherapy can act at different levels to improve radioresponsiveness. These include decreasing the accumulation and inhibition of repair of sublethal or potentially lethal damage, perturbing the cell cycle kinetics, and inhibiting cell repopulation thus modifying the dose response curve [14]. Chemotherapy can also decrease tumor bulk and improve blood supply, thus improving reoxygenation and radiation response. This is particularly relevant for neoadjuvant chemotherapy in large tumors. Neoadjuvant chemotherapy could also have an impact on micrometastatic tumor and identify patients who have chemoresponsive disease.

On the other hand, potential drawbacks of using neoadjuvant chemotherapy are delay in applying effective radiotherapy, induction of resistant clones of tumor cells, progression of disease in nonresponders, and potential increased toxicity leading to interruptions in definitive radiotherapy [4, 19, 35, 37]. In our study, the time required for chemotherapy was compressed to four weeks, which in theory, can reduce the possibility of accelerated repopulation of tumor cells during definitive radiation. The lack of clear benefit from this combination, however, indicates that other mechanisms could be involved such as tumor clone selection. It is also possible that accelerated tumor cell repopulation may still occur despite this overall time reduction. Reports of similar studies in the literature are conflicting. Sardi *et al.* evaluated this regimen before radical surgery and reported that it is feasible, with increased resectability rates, and encouraging overall results [39, 40]. In contrast, Leborgne *et al.* found no long-term benefit of this same regimen evaluated in a randomized study versus radiation alone [21].

Another drawback from neoadjuvant chemotherapy particularly when good responses are obtained is patient refusal to continue with further therapy. Almost invariably, those patients develop recurrence and die with untreatable progressive disease. Two patients in our series had a complete clinical response with resolution of all symptoms and decided against further therapy. They presented later with extensive recurrence and could not be salvaged with radiotherapy.

Several reports have indicated that cervical cancer frequently responds to various chemotherapeutic agents including cisplatin, 5 FU, bleomycin, vincristine, hydroxyurea, and more recently paclitaxel. Despite the abundance of such reports, there is no proof yet of improved overall survival. In an early nonrandomized study, Sardi *et al.* reported that the response to neodajuvant chemotherapy was strongly correlated with the initial tumor volume, and patients with larger tumors did better if they underwent subsequent surgery rather than radiation [39]. This study however, was not randomized and was riddled with confounding variables. In a recent report, Sardi *et al.* presented results of a randomized study comparing radiotherapy with or without prior surgery vs neoadjuvant chemotherapy followed by the same therapy [40]. They found a significant difference in favor of the neoadjuvant treatment in the group of patients undergoing surgery. This was attributed to a beneficial effect of neoadjuvant

chemotherapy on pathologic downstaging and resectability rates. In contrast, Kumar *et al.*, in a randomized trial, showed no difference in overall disease-free survival of patients with locally advanced cervical cancer treated with radiotherapy alone or with neoadjuvant chemotherapy followed by radiotherapy [19]. A similar finding was reported by Chang *et al.* on patients treated by neoadjuvant chemotherapy followed by surgery vs radiation therapy alone [5]. Several other comparative studies have also shown no real benefit from neoadjuvant chemotherapy [6, 7, 21, 43, 44, 45]. In a comparable fashion, the value of adjunctive chemotherapy was also extensively evaluated in head and neck cancer, a disease which shares many features with cervical cancer, particularly with regard to histology, response to radiation, and a tendency for primary locoregional growth and orderly spread. Although not directly applicable to cervix cancer, studies on adjunctive chemotherapy for non-nasopharyngeal squamous cell carcinomas of the head and neck, have repeatedly shown no benefit from neoadjuvant chemotherapy [2, 15, 25, 29, 32], whereas concurrent chemoradiation was found more promising in both randomized studies and large meta-analyses [1, 4, 10, 26].

Because of the inconsistency and disappointing results of neoadjuvant chemotherapy studies in cervix cancer, a growing interest has developed in concurrent chemotherapy and led to several studies using concurrent chemoradiation for definitive or postoperative adjuvant therapy. Recently, three studies have reported that concurrent radiotherapy with chemotherapy, especially cisplatin and 5-FU, significantly improved the control of pelvic disease and prolonged survival in high-risk Stage IB or more advanced Stages IIB-IV [17, 27, 34]. Keys *et al.* compared radiotherapy alone versus radiotherapy concurrently with weekly cisplatin in 369 patients with bulky Stage IB and found better pelvic control with prolonged survival in the chemotherapy arm [17]. Rose *et al.* compared radiotherapy with weekly cisplatin to radiotherapy with cisplatin, hydroxyurea and fluorouracil in 526 patients with Stages IIB-IVA [34]. They reported a survival advantage with less toxicity with the cisplatin arm. Finally, Morris *et al.* reported the Radiation Therapy Oncolgy Group (RTOG) 90-001 study which randomized 388 patients with advanced stages cervical cancer, IB (bulky)-IVA or presence of documented pelvic lymph nodes, to three cycles of cisplatin and 5FU with concurrent pelvic and intracavitary radiotherapy versus pelvic-paraaortic and intracavitary radiotherapy [27]. They found a significant improvement in pelvic control and overall survival with the use of concurrent chemotherapy. These last three trials prompted the National Cancer Institute to issue a clinical announcement that " strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation in women who require radiation therapy for cervical cancer" [28]. Reviewing all the available data, Thomas also recommended using platinum-based concurrent chemotherapy along with radiotherapy [46]. This was corroborated by a recent meta-analysis that revealed that concurrent chemoradiation provides an absolute 12% survival benefit over standard radiation alone for carcinoma of the cervix [13]. However, although this wealth of evidence seemed quite indisputable with cisplatinum-based concurrent therapy becoming the new standard of care, recent randomized data from Yale University showed that single agent mitomycin-c might also be as effective for concurrent therapy [33]. In addition, a large trial by the National Cancer Institute-Canada failed to reveal any advantage of weekly single agent cisplatinum with radiotherapy over optimal radiation therapy alone [30]. This latter trial has somewhat tempered the prevailing enthusiasm and reopened the question of what is the best chemotherapy agent and timing for chemoradiation for carcinoma of the cervix [22].

There are no prospective studies comparing neoadjuvant chemotherapy to concurrent chemotherapy. However, because of the reported improved survival advantage for patients on concurrent chemotherapy in several trials which was confirmed by the recent meta-analysis [13], one cannot but recommend the judicious use of platinum-based concurrent chemotherapy with radiotherapy for patients with advanced cervical cancer. Until more comparative data is available, neoadjuvant chemotherapy may be reserved for patients in whom radiotherapy is contraindicated and/or surgery is a better option (such as patients with pelvic inflammatory disease, prior irradiation, active scleroderma, genetic radiosensitive syndromes, or advanced and symptomatic diverticulitis, etc.). For these patients, neoadjuvant chemotherapy may make surgery easier or more feasible. This intensive course of neoadjuvant chemotherapy as used in our study, appears to be well tolerated, it is relatively of short duration and in well informed patients should not introduce extensive delays in effective treatment.

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