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Paclitaxel plus oxaliplatin for recurrent or metastatic cervical cancer: A New York Cancer Consortium study

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Objectives: Significant progress has been made in the treatment of locally advanced cervical cancer (CC); however, the management of recurrent and metastatic CC remains inadequate. Cisplatin (CDDP) is an effective radiosensitizer, but its single-agent activity in patients with advanced and recurrent CC, is disappointing, especially in patients previously treated with CDDP, with a best response rate of 13% (Long, J Clin Oncol 2005). Oxaliplatin has preclinical activity in CDDP-resistant tumors, is active in colorectal cancer (a tumor not responsive to CDDP) and may have synergy with paclitaxel.
Methods: Patients with recurrent or metastatic CC who had no prior chemotherapy except primary concurrent CDDP/radiation were treated with intravenous paclitaxel 175 mg/m^2 and intravenous oxaliplatin 130 mg/m^2 every 21 days. Response, as determined by RECIST criteria and confirmed every nine weeks, and toxicity were the primary outcomes. This is the completed data analysis of a standard Simon two-stage phase II study.
Results: Of the 35 patients enrolled, 33 were treated. One patient died of cardiac arrest unrelated to treatment after one dose, leaving 32 evaluable patients. Median age was 56 (27-78); 30 had had prior radiation (23 with CDDP). Patients completed a mean of four cycles (range: 1-8). Two patients had a complete response and five had a partial response, for a total response rate of 7/32 (22%). There were also eight patients with stable disease (<30% decrease and 20% increase in consecutively documented target lesions) for an overall clinical benefit rate of 15/32 (47%). In patients who had clinical benefit, the mean time to best response was 10 weeks (range: 6-23) and the mean time to progression was 44 weeks (range: 9-181). A total of 126 cycles of paclitaxel and oxaliplatin were administered. There were 16 (12.7%) grade 3/4 hematologic toxic effects and 25 (19.8%) grade 3/4 nonhematologic toxic effects. One patient had a hypersensitivity reaction to paclitaxel. There were six dose reductions: three dose reductions were due to grade 3 neuropathy, one due to grade 3 thrombocytopenia, one due to a recurrent electrolyte imbalance, and one due to hematologic toxicity. There were no treatment-related deaths.
Conclusions: The combination of paclitaxel and oxaliplatin is an effective regimen in patients with recurrent or persistent CC and is reasonably well tolerated. Comparison with CDDP or carboplatin-based regimens is warranted.

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Prognostic relevance of carbonic anhydrase IX in high-risk, early-stage cervical cancer: A Gynecologic Oncology Group study

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Objectives: The purpose of this study was to determine whether carbonic anhydrase IX (CA-IX) is associated with progression-free survival (PFS) and overall survival (OS) in women with high-risk, early-stage cervical cancer treated with adjuvant pelvic radiotherapy with or without radiosensitizing chemotherapy on a multicenter randomized phase III trial (SWOG 8797/GOG 109/RTOG 91-12).
Methods: CA-IX expression was detected using an immunohistochemistry assay with M75 antibody and categorized as low (≤80% CA-IX-positive tumor cells) or high (>80% CA-IX-positive tumor cells). Associations between CA-IX and clinical characteristics or outcome were evaluated, and the relationships between CA-IX and angiogenic markers were explored.
Results: High CA-IX expression was observed in 35 of 166 (21.1%) cases. Categorized CA-IX was not associated with age, race, stage, cell type, grade, positive margins, parametrial extensions, positive lymph nodes or lymphovascular space invasion, but was directly associated with tumor size categorized as <2, 2-2.9, or ≥3 cm (P=0.005) and cervical invasion categorized as within the inner two-thirds or the outer third of the cervix (P=0.027). Women with high versus low CA-IX expression had slightly worse PFS (P=0.053) and significantly worse OS (P=0.044). After adjustment for prognostic clinical covariates, high CA-IX expression was an independent prognostic factor for PFS (HR=1.996, 95% CI=1.072-3.715, P=0.029) and OS (HR=2.575, 95% CI=1.314-5.049, P=0.006). CA-IX was not associated with immunohistochemical expression of p53, CD-31, CD-105, thrombospondin 1 or vascular endothelial growth factor.
Conclusions: Tumor hypoxia measured by immunohistochemical expression of CA-IX is an independent prognostic factor for both PFS and OS in high-risk, early-stage cervical cancer.

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Concurrent chemotherapy and extended-field, intensity-modulated radiotherapy for cervical cancer: Updated results with extended follow-up

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Objectives: The purpose of this article was to report on the clinical outcomes of concurrent cisplatin and extended-field, intensity-modulated radiotherapy (EF-IMRT) for cervical carcinoma with extended follow-up.

Methods: Forty-one patients with stage 1B2-IVA cervical cancer were treated with EF-IMRT and concurrent chemotherapy followed by high-dose-rate brachytherapy (HDRB) between 2001 and 2007 (Table 1). Pelvic lymph node involvement was observed in 24 patients, and 10 of these patients had paraaortic nodal disease. Treatment volume included the cervix, uterus, parametria, presacral space, upper vagina, and pelvic, common iliac, and paraaortic nodes to the T12-L1 interspace. Patients were assessed for acute toxicity according to the NCI Common Toxicity Criteria for Adverse Events, Version 3.0 (Table 2). All late toxicity was scored with the Radiation Therapy Oncology Group late toxicity score (Table 3).

Results: All patients completed the prescribed course of EF-IMRT. All but one patient received HDRB. Median treatment time was 51 days. Acute grade ≥ 3 gastrointestinal toxicity, genitourinary toxicity, and myelotoxicity were observed in 1, 1, and 12 patients, respectively. Thirty-nine patients (95%) had a complete response to treatment. At the median follow-up of 37 months (range: 4-82), 15 patients (36%) developed a recurrence or progressive disease (local 3, regional 1, systemic 8, and systemic and locoregional 3) (Table 4). Five-year actuarial locoregional control, recurrence-free survival, and overall survival rates were 77.9, 61, and 62%, respectively. The grade ≥ 3 toxicity rate for the entire cohort was 8%. Table 5 summarizes the relationship between recurrence pattern and FIGO stage.

Conclusions: Our long-term follow-up in patients treated with EF-IMRT and concurrent chemotherapy demonstrated it to be well tolerated with acceptable acute and late toxicity. Locoregional control was good, with distant metastasis predominating as the most common mode of failure.

Table 1
Patient characteristics

Number	41
Age	41.5 (26-69)
FIGO stage	
IB2	11
IIA	2
IIB	21
IIIB	6
IVA	1
Tumor size	5 (3-11)
Histologic type	
Squamous	30
Adenosquamous	4
Adenocarcinoma	2
Other	5
Lymph node status	
Pelvic	24
Pelvic and paraaortic	10

Table 2
Acute toxicity graded according to the NCI Common Toxicity Criteria for Adverse Events, Version 3.0

	Toxicity grade				
	0	1	2	3	4
Genitourinary (dysuria/nocturia)	17	16	7	1	0
Gastrointestinal					
Proctitis	31	8	2	0	0
Diarrhea	4	5	32	0	0
Anorexia	19	18	4	0	0
Nausea/vomiting	10	5	25	1	0
Bone marrow	5	8	15	12	1

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TP53 restoration using E6/E7 small interfering RNA potentiates the therapeutic effect of cisplatin in cervical squamous cell carcinoma

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Objectives: The purpose of this study was to investigate the potential effect of human papillomavirus (HPV) E6 small interfering RNA (siRNA) as a chemosensitizer and its synergistic effect on HPV-positive cervical squamous cell carcinoma treated with concurrent cisplatin (CDDP) chemotherapy.

Methods: E6-specific siRNA was transfected into HeLa, SiHa, and CaSki cells, which were then treated with CDDP. Flow cytometry and senescence-associated β-galactosidase (SA-β-Gal) assay was performed to analyze the effect of siRNA. An in

vivo xenograft model was established by subcutaneous injection of HeLa-luc cells into nude mice. Bioluminescence quantification and immunohistochemistry were used to confirm the in vivo effect of siRNA.

Results: First, we confirmed that HPV18 E6 siRNAs achieved target-specific gene silencing without off-target effects and an interferon response. In an in vitro experiment, long-term combination therapy with HPV18 E6/E7 siRNA and CDDP synergistically suppressed cell growth and induced apoptosis and SA-β-Gal staining. In a xenograft model, concurrent CDDP chemotherapy and HPV18 E6/E7 siRNA treatment suppressed tumor growth through apoptosis, senescence, and antiangiogenesis. These in vitro and in vivo effects of combined therapy were significantly higher than those of either CDDP or HPV18 E6/E7 siRNA treatment.

Conclusions: These results indicate that combined CDDP and synthetic HPV E6/E7 siRNA treatment synergistically augments their therapeutic effect on cervical squamous cell carcinoma and highlight the potential use of synthetic E6/E7 siRNA as a chemosensitizer in combination therapy.

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Single-nucleotide polymorphisms in MMP9 and SIPA1 are associated with increased risk of nodal metastases in early-stage cervical cancer

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Objectives: Growing evidence supports the notion that heritable germline polymorphisms may modulate metastatic efficiency in cancer. MMP9 is a proteolytic enzyme implicated in tumor invasion, angiogenesis and growth; single-nucleotide polymorphisms (SNPs) and their catalytic component (rs17576) have been associated with nodal metastases in gastric cancer. SIPA1 is a activating protein involved in mitogen-induced cell cycle regulation, in which exonic (rs746429) and promoter (rs931127) SNPs have been associated with nodal metastases in breast cancer. The aim of this study was to determine whether these three functional SNPs are associated with nodal metastases in patients with stage Ib-IIa cervical cancer.

Methods: Consecutive patients with stage Ib1-IIa cervical cancer who underwent complete pelvic lymph node dissection and contributed blood to a cervical cancer tissue bank were included in this case-control study. Cases were identified as patients with at least one positive lymph node ($n=101$) and matched with controls with negative nodes ($n=273$). Genotyping was performed on genomic DNA using an Applied Biosystems assay with validated primers to SNPs in MMP9 (rs17576) and SIPA1 (rs746429, rs931127). The distribution of each SNP was correlated with clinical variables. Data were analyzed using the $\chi^{2/}$ and Fischer's exact test.

Results: No statistically significant difference was found in allelic distribution between cases and controls overall for any of the three SNPs, though the association between the GG genotype (rs931127) and nodal metastases approached significance in SIPA1 (OR=1.23, $P=0.07$). After controlling for stage, associations were present in each of the three SNPs. In stage IB2 patients ($n=53$), all five patients with the MMP9 GG genotype (rs17576) had positive nodes compared with no controls and having at least one G allele increased a patient's risk of nodal metastases (OR=3.2, $P=0.017$). In stage IB1 patients ($n=304$), in both SIPA1 SNPs, the G allele was associated with an increased risk of nodal metastases (rs76329 AG + GG: OR=10.3, $P=0.003$; rs931127 AG+GG: OR=2.3, $P=0.0012$). After controlling for lymphvascular space invasion (LVSI), significant associations existed in both SIPA1 SNPs in patients with no LVSI ($n=160$). At rs76329, the G allele was associated with a higher risk of nodal metastases (GG: OR=6.1, $P=0.042$) and all patients with the AA genotype had negative nodal sampling. At rs931127, the GG genotype was also associated with an increased risk of nodal disease (OR=4.5, $P=0.016$).

Conclusions: In this case-control study, the distribution of functional SNPs in MMP9 and SIPA1 differed statistically between cervical cancer patients with and those without nodal metastases after controlling for stage and LVSI. The LVSI association is particularly noteworthy as this may support alternative mechanisms of tumor spread. Although this is the largest such study to date, further work is warranted investigating the role of these and other SNPs in metastatic susceptibility in cervical cancer.

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Multiple-type human papillomavirus (HPV) infections: An analysis of prevalence and frequency of specific types in 73,000 women referred for HPV testing at the time of cervical cytology

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Objectives: There is limited data addressing the epidemiology of multiple-type cervical HPV infections. Prophylactic vaccine trials report a low frequency of multiple-type infections. Our objectives were to (1) determine the frequency of multiple-type infection, and (2) determine if any types are identified in multiple infections more or less frequently than might be expected under the independence assumption.

Methods: This is a retrospective analysis of women from one of 23 laboratories using type-specific HPV testing. Descriptive statistics were used to determine the rate of HPV infection by type. Two-type infection rates for each combination were calculated and the independence of the types was tested using χ^2 and Fisher's exact tests. A post hoc Bonferroni adjustment was used for multiple tests and P values less than 0.001 were considered statistically significant, with which a simultaneous significance level of 0.05 was ensured.

Results: HPV typing was performed on 73,563 women referred on the basis of their cytological screening results (Table 1). HPV infection was present in 31.2% of patients. Multiple-type HPV infection was present in 25.1% of positive participants, with type 16 present in 30.0% of these. The remaining most frequent types involved, in decreasing order of frequency, were 53, 52, 31, 66, 6, 18, and 11 (Table 2). Of the total participants with multiple infections, 82.6% had infections with two types. For the eight listed types (most notably HPV16), all were less likely to be found in multiple infections than would be expected by the frequency of each type alone under the assumption of independence. Next, we considered the frequency of multiple-type infection based on phylogenetic virus species (Table 3). The α9 species (types 16, 31, 33, 35, 52, 58, and 67) was most frequent, being involved in 57.8% of multiple infections. We also considered whether multiple-type infections were more likely to involve types within a phylogenetic species or between phylogenetic species. For all phylogenetic virus species except α9, both types in two-type multiple infections were less likely than expected to be from the same virus species. In contrast, in participants with two-type infections in which one type was from species α9, it was more likely than expected that the second type was also from α9 ($P<0.0001$).

Conclusions: Multiple-type HPV infections were present in 25.1% of HPV-positive women. There may be a competitive interaction between HPV types leading to less frequent involvement in multiple infections than would be expected if multiple infection was independent of HPV type. In particular, HPV type 16 is involved in fewer multiple infections than expected. HPV phylogenetic virus species α9, which includes type 16, appears to have an affinity for co-infection with another type from α9 in patients with multiple infections.

Table 1
Patient population and overall multiple infection rates

	N	%
Total population	73,563	
Total positive for HPV	22,926	31.2
Total with multiple infections	5,747	25.1
Infection with two types	4,749	82.6
Infection with three types	897	15.6
Infection with four types	101	1.76

Table 2
Rates of infection (among 22,926 positive participants) and involvement in multiple infections (among 5747 participants) by type

Virus type	*N*	%
Type 6		
Rate in positive participants	1280	5.6
Rate in multiple infections	575	10.0
Type 11		
Rate in positive participants	534	2.3
Rate in multiple infections	202	3.5
Type 16		
Rate in positive participants	4520	19.7
Rate in multiple infections	1724	30.0
Type 18		
Rate in positive participants	881	3.8
Rate in multiple infections	393	6.8
Type 31		
Rate in positive participants	1757	7.7
Rate in multiple infections	654	11.4
Type 52		
Rate in positive participants	2013	8.8
Rate in multiple infections	872	15.2

Table 2 (*continued*)

Virus type	*N*	%
Type 53		
Rate in positive participants	2495	10.9
Rate in multiple infections	1099	19.1
Type 66		
Rate in positive participants	1662	7.3
Rate in multiple infections	655	11.4

Table 3
Rates of infection (among 22,926 positive participants) and involvement in multiple infections (among 5747 participants) by virus species

Virus species	*N*	%
α1		
Rate in positive participants	72	0.3
Rate in multiple infections	32	0.6
α3		
Rate in positive participants	4897	21.4
Rate in multiple infections	2204	38.1
α5		
Rate in positive participants	1017	4.4
Rate in multiple infections	512	8.9
α6		
Rate in positive participants	4486	19.6
Rate in multiple infections	1800	31.3
α7		
Rate in positive participants	3729	16.3
Rate in multiple infections	1600	27.8
α8		
Rate in positive participants	5	0.02
Rate in multiple infections	2	0.03
α9		
Rate in positive participants	9825	42.9
Rate in multiple infections	3320	57.8
α10		
Rate in positive participants	1945	8.5
Rate in multiple infections	807	14.0
α11		
Rate in positive participants	360	1.6
Rate in multiple infections	132	2.3
α13		
Rate in positive participants	710	3.1
Rate in multiple infections	337	5.9
α15		
Rate in positive participants	356	1.6
Rate in multiple infections	158	2.8

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Screening for cervical cancer using primary human papillomavirus testing and reflex cytology: A cost-effective analysis

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Objectives: The purpose of the study described here was to evaluate the cost-effectiveness of using human papillomavirus (HPV) testing as a primary screening modality for cervical cancer compared with routine screening via cervical cytology.
Methods: A decision analysis that simulates the natural history of HPV infection and cervical cancer was developed to compare three cervical cancer screening strategies: (1) HPV testing with reflex cytology for patients positive for high-risk HPV, (2) simultaneous HPV testing and cytology, and (3) cytology with reflex HPV testing for atypical squamous cells of undetermined significance (ASCUS) cytology. Cost-effectiveness was examined from the payer's perspective, examining only direct costs for screening and treatment. Markov models were developed to fully capture missed cases (false negatives). These models followed a cohort of 30-year-old women through 15 two-year cycles with one screening per cycle.
Results: The test screening strategy, HPV testing with reflex cytology, proved to be the least costly strategy at $1056 per 1.39 cancer cases averted (CCA). The test strategy dominated the other two strategies with a cost-effectiveness ratio of $762 per CCA. Cytology with reflex HPV for ASCUS cost $1302 per 0.952 CCA, and the most costly strategy was HPV and cytology together at $1385 per 0.977 CCA. Multiple one-way sensitivity analyses confirmed the robustness of this study.
Conclusions: Cervical cancer screening using primary HPV testing with reflex cytology for patients positive for high-risk HPV is more cost-effective than current screening modalities.

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Trends in vaginal carcinoma incidence and survival

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Objectives: The purpose of this study was to determine if vaginal cancer incidence and survival have changed over the last three decades.
Methods: The Surveillance Epidemiology and End Results database was used to access trends in vaginal cancer incidence and survival from 1973 to 2005. The incidence rates by age and stage were calculated and tested for trends over time. One- and five-year survival rates were calculated and tested for trends over time.
Results: A total of 8242 cases were identified: 3193 (39%) in situ and 5049 (61%) invasive. Of the invasive cases, 1453 (29%) were localized, 946 (19%) were regional, 740 (15%) were distant, and 702 (14%) were unstaged. The distribution of stages did not differ significantly over time. The overall age-adjusted rate for vaginal carcinoma was 0.77 cases per 100,000 women. The rate for in situ disease was 0.30 and that for invasive disease was 0.43. Invasive cancer risk increased as a woman aged, from a rate of 0.02 among women <10 years old to 3.15 among women ≥ 80 years. The risk of in situ carcinoma increased until age 70-79 and then decreased. These trends did not differ significantly over time. The incidence rate for vaginal carcinoma increased 87% from 1973 to 2005. The rate of in situ disease increased 347%, and the rate of invasive disease decreased by 12%. The incidence of squamous cell carcinoma increased 135% during the years examined, with a

566% increase in in situ disease and a 3% decrease in invasive disease. Among women with invasive disease, one-year survival was 73.8%, and five-year survival was 41.9%, with a median overall survival of 39 months. One-year survival for women with squamous cell histology was 75.7%, and fvie-year survival was 43.7% with a median overall survival of 44 months. Survival rates did not differ significantly over time. Women with localized disease had a one-year survival rate of 87.0%, comparedwith to 77.4% for women with regional disease, 56.1% for those with distant disease and 59.8% for unstaged women. Five-year survival rates for these groups were 58.3, 43.6, 20.4 and 29.3%, respectively.

Conclusions: This is the first population-based study to examine incidence and survival trends for vaginal cancer in the United States. Incidence of vaginal carcinoma increases as women age, although the rate of in situ disease peaks among women aged 70-79. Distribution of stage and age at diagnosis has not changed over time. Survival has not changed significantly over time. The incidence of vaginal carcinoma is increasing, however this is due to a large increase in the incidence of in situ disease, as the incidence of invasive disease has decreased slightly. Possible etiologies for the increase in incidence include improved detection or increased prevalence of human papillomavirus (HPV). The discrepancy between the rates of in situ and invasive disease may be due to the long lead time for developing invasive vaginal cancer. If so, the rate of vaginal cancer may substantially increase in the coming years.