# Treatment options in recurrent cervical cancer (Review)

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**Abstract.** The management of recurrent cervical cancer depends mainly on previous treatment and on the site and extent of recurrence. Concurrent cisplatin-based chemo-radiation is the treatment of choice for patients with pelvic failure after radical hysterectomy alone. However, the safe delivery of high doses of radiotherapy is much more difficult in this clinical setting compared with primary radiotherapy. Pelvic exenteration usually represents the only therapeutic approach with curative intent for women with central pelvic relapse who have previously received irradiation. In a recent series, the 5-year overall survival and operative mortality after pelvic exenteration ranged from 21 to 61% and from 1 to 10%, respectively. Free surgical margins, negative lymph nodes, small tumour size and long disease-free interval were associated with a more favourable prognosis. Currently, pelvic reconstructive procedures (continent urinary conduit, low colorectal anastomosis, vaginal reconstruction with myocutaneous flaps) are strongly recommended after exenteration. Concurrent cisplatin-based chemo-radiation is the treatment of choice for isolated para-aortic lymph node failure, with satisfactory chances of a cure in asymptomatic patients. Chemotherapy is administered with palliative intent to women with distant or loco-regional recurrences not amenable by surgery or radiotherapy. Cisplatin is the most widely used drug, with a response rate of 17-38% and a median overall survival of 6.1-7.1 months. Cisplatin-based combination chemotherapy achieves higher response rates (22-68%) when compared with single-agent cisplatin, but median overall survival is usually less than one year. In a recent Gynecologic Oncology Group (GOG) trial the combination topotecan + cisplatin obtained a significantly longer overall survival than single-agent cisplatin in patients with metastatic or recurrent or persistent cervical cancer. A subsequent GOG study showed a trend in terms of longer overall survival and better quality of life for the doublet cisplatin + paclitaxel vs. the doublets cisplatin + topotecan, cisplatin + vinorelbine, and cisplatin + gemcitabine. Molecularly targeted therapy may represent a novel therapeutic tool, but its use alone or in combination with chemotherapy is still investigational.

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## 1. Introduction

Cervical cancer is the second most common malignancy in women with an estimated 493,000 new cases and 274,000 deaths in 2002 (1). Although radical surgery and radiotherapy represent effective treatment modalities, up to one third of patients will develop progressive or recurrent tumours, the pelvis being the most common site of failure (2-4). The relapse rate of cervical cancer ranges between 11 and 22% in FIGO stages Ib-IIa and between 28 and 64% in FIGO stages IIb-IVa (5).

The management of recurrent cervical cancer depends mainly on previous treatment and on the site and extent of recurrence (3-5). Up to 70% of patients receive pelvic radiotherapy at some point in their treatment, and tumour failure in an irradiated pelvis is usually associated with a dismal prognosis. Cervical cancer recurrences can be central pelvic, lateral pelvic and extra-pelvic (6,7). Central pelvic recurrence develops from the cervix and vagina after primary radiotherapy or from the vaginal cuff and central scar after radical hysterectomy. This relapse can be limited to the vaginal vault or can more often involve the bladder and/or rectum. Lateral pelvic recurrence includes parietal and visceral pelvic side disease. The former consists of pelvic

lymph node metastases and is usually located above the level of the obturator nerve, whereas the latter originates from the paracervix or from scars of the paracervical resection and is placed below the obturator nerve. The most common extra-pelvic metastases involve para-aortic lymph nodes, lungs, liver and bone (8-10).

An Italian multicenter retrospective study including 327 consecutive women with recurrent cervical cancer showed that 120 patients (36.7%) had recurrent disease in the central pelvis, 67 (20.5%) on the vaginal vault, 31 (9.5%) in the lateral pelvis, 16 (4.9%) in lymph nodes, 79 (24%) in distant sites and 14 patients (4.3%) both in distant sites and in the pelvis (10).

## 2. Central or lateral pelvic recurrence in patients primarily treated with radical hysterectomy without adjuvant irradiation

Irradiation or concurrent cisplatin-based chemo-radiation is the treatment of choice for patients with pelvic recurrence after radical hysterectomy alone (3,4,11-18). However, the safe delivery of high doses of radiotherapy is much more difficult in this clinical setting compared with primary radiotherapy, since brachytherapy options are limited to treatment of the vaginal vault alone and since the presence of post-surgical adhesions increases the radiation dose to the bowel (19,20). Data from the literature report 5-year survival rates ranging from 6 to 77%, mainly dependent on the site of relapse (4,13). In the series of Ijaz *et al* (13), patients with vaginal recurrence or paravaginal extension without pelvic wall involvement had a 5-year survival of 69 vs. 18% for those with central recurrence with pelvic wall extension. Similarly, in the study of Jain *et al* (17) the 5-year disease-specific survival was 55.4% for women with a vault relapse and 12.5% for those with lymph node recurrence. Vaginal vault relapse, which can be managed with external irradiation plus brachytherapy, is more effectively treated than nodal disease which receives external irradiation alone. Moreover, lymph node metastases can be often associated with a systemic spreading of disease.

An important novel treatment modality is represented by intensity-modulated radiotherapy (IMRT) that can allow the delivery of differential doses of radiation to a given target volume. Mundt *et al* (21) delivered pelvic IMRT to 15 women with cervical or endometrial cancer, with excellent target volume coverage, considerable sparing of normal tissues, and less acute gastrointestinal sequaelae compared with conventional pelvic irradiation. Clinical investigation on IMRT combined with chemotherapy is strongly warranted to attempt better control of advanced or recurrent cervical cancer (17).

## 3. Central pelvic recurrence in patients who previously received irradiation

Radical hysterectomy has been sometimes employed in patients with small persistent/recurrent cervical cancer after primary radiotherapy, with 5-year survival rates ranging from 27 to 72% and with a high rate of complications (22-27). Rubin *et al* (23) reassessed 21 radical hysterectomies performed at Memorial Sloan-Kettering Cancer Center for recurrent cervical cancer. Two patients (9.5%) died after surgery due to sepsis, 10 (48%) developed postoperative fistulas, and 13 (62%) survived with a median follow-up of 73 months. The disease relapsed in none of the 11 women with tumour diameter ≤2 cm at the time of surgery and in 7 (70%) of the 10 patients with larger tumour size. In the study of Coleman *et al* (26), 42% of the 50 patients experienced severe complications, mainly represented by urinary tract injuries, and the 5- and 10-year actuarial survival rates were 72 and 60%, respectively. Tumour size at the time of radical hysterectomy was significantly related to the clinical outcome; the 5-year actuarial survival was 90% for women with a lesion diameter <2 cm compared with 64% for those with larger lesions ($p<0.01$). All 5 patients with lymph node metastases died of disease after a median interval of 13 months from surgery. Maneo *et al* (27) reassessed 34 patients who underwent radical hysterectomy for persistent or recurrent disease after primary radiotherapy. Grade III-IV complications occurred in 15 (44%) cases; in detail, 5 (15%) patients experienced a fistula. Actuarial 5-year survival was 49% for the entire group, 65% for patients with FIGO stage Ib-IIa primary disease, no preoperative clinical parametrial involvement, and recurrent/persistent tumour ≤4 cm, vs. 24% for those who did not fit these criteria ($p=0.01$). Therefore, radical hysterectomy should be taken into consideration only in highly selected cases, with small persistent/recurrent lesions limited to the cervix.

Pelvic exenteration usually represents the only therapeutic approach with curative intent for patients with central pelvic failure who have previously received irradiation. The original classification of pelvic exenteration into three groups, i.e., anterior, posterior and total, addresses only the nature of the pelvic viscera removed. Magrina *et al* (28,29) and Chiva *et al* (30) have suggested a new subclassification into type I (supra-levator), type II (infralevator) and type III (with vulvectomy), which takes the levator ani muscle as a reference point and which offers a better definition of the extent of resection and the anatomical changes associated with each operation. From 1950 to 1970 pelvic exenteration achieved 5-year overall survival rates of 20-42% for patients who had no other therapeutic options (31-36). However, operative mortality ranged from 10 to 26%, and severe complications were very frequent. Patients usually underwent an incontinent Bricker ileal conduit as a urinary diversion and a terminal colostomy. The more stringent the patient selection criteria (central disease, no para-aortic involvement, no peritoneal disease), the greater the chance for a favourable clinical outcome (30).

In more recent series, the 5-year overall survival and operative mortality ranged from 21 to 73% and from 1 to 10%, respectively (29,37-43). Free surgical margins (37-39,41,43), negative lymph nodes (35,37,43), small tumour size (38) and long disease-free interval (37-39) were associated with a more favourable prognosis. For example, Marnitz *et al* (39) reported that survival correlated with the disease-free interval (5-year survival of 16.8, 28 and 83.2% for an interval <2 years, 2-5 years and >5 years, respectively; $p=0.01$) as well as with the status of surgical margins (2-year survival of 10.2% for positive margins vs. 5-year survival of 55.2% for negative ones; $p=0.006$). Fleisch *et al* (43) reported that the 5-year survival was 42% for patients with complete resection, no lymph node involvement and no sidewall infiltration vs. 12% for those who did not have one or more of these findings. According

to Shingleton *et al* (38) the best candidates for cure by pelvic exenteration were the patients with recurrent small (<3 cm), mobile central tumours and with a disease-free interval of one year or longer.

Morley *et al* (37) found that the 5-year survival was 73% for patients with squamous cell carcinoma and 22% for those with adenocarcinoma, whereas other authors failed to detect a significant difference in the clinical outcome according to the histological type (39,40,42).

The clinical improvements obtained in the last decades are mainly due to better surgical techniques, more intensive postoperative care and a better definition of patient selection criteria made easier by the availability of new diagnostic techniques (44-50). Currently, positron emission tomography (PET)/computed tomography (CT) should be the first imaging technique used to rule out the presence of extra-pelvic disease (50). Distant metastases, with very few exceptions, exclude a chance of cure, whereas regional metastases significantly decrease but, especially if in a low number, do not completely abolish a curative therapeutic option (6,51).

However, despite a very thorough preoperative investigation, inoperable disease is often detected at the time of laparotomy. Some authors have proposed the use of laparoscopy in screening suitable candidates for exenteration (47,52,53). This approach can prevent unnecessary laparotomies, shorten the hospital stay and the postoperative recovery and contribute to a better quality of life for women with inoperable disease.

At present, pelvic reconstructive procedures are strongly recommended after exenteration. An ileocolonic segment is currently employed for continent urinary diversion (54-59). The continent cutaneous reservoir, which uses the terminal ileum or the appendix as an outlet, avoids the need for a urostomy appliance, protects the upper urinary tract and allows relatively easy emptying by intermittent catheterisation, with effective day and night continence. However, continent urinary diversion is not free from postoperative complications. Among 77 patients who underwent the creation of the Miami urinary pouch, the most common complications were ureteral stricture/obstruction (22%), difficult catheterisation (20%) and pyelonephritis (17%) (58).

The patients who undergo a supralevator pelvic exenteration are candidates for a low colorectal anastomosis by staple devices which avoids a colostomy and significantly improves the quality of life. However this surgical procedure may have some risks in irradiated patients (41,59,60). In the series of Angioli *et al* (58), 33% of the irradiated patients developed anastomotic breakdown or fistula, whereas these complications occurred only in 7.5% of the nonirradiated patients, and a protective colostomy failed to improve the healing rate of the anastomosis. A temporary ileostomy could be taken into consideration since it protects both colorectal anastomosis and the small bowel anastomosis that closes the donor area for the urinary conduit (30).

Pelvic floor and vaginal reconstruction with myocutaneous flaps are frequently proposed in order to reduce postoperative complications and especially gastro-intestinal fistulas, to preserve the psychosocial well-being of the woman and sexual activity, and to improve the quality of life (40,61-63). Goldberg *et al* (40) reported that 20 out of 36 patients (56%) who had vaginal reconstruction with vertical rectus abdominis myocutaneous flaps were sexually active.

Intra-operative irradiation therapy (IORT) can be added particularly in the presence of microscopically positive margins on frozen-section analysis (3,64,65). Different ways of delivering IORT have been proposed, from external beam irradiation to high-dose-rate intraoperative brachytherapy and even to delayed brachytherapy after placement of low-dose-rate vectors after surgery (66).

## 4. Lateral pelvic recurrence in patients who previously received irradiation

Patients with recurrent cervical cancer involving the pelvic side wall are traditionally unfit for exenteration and usually receive palliative chemotherapy when the primary therapy was (chemo-) radiation or surgery plus adjuvant irradiation.

Höckel has proposed a novel surgical approach for these patients, termed laterally extended endopelvic resection (LEER) (67). This operation is characterized by the inclusion of the internal iliac vessel system, endopelvic part of the obturator internus muscle, coccygeus, ilio-coccygeus and pubo-coccygeus muscles at the side of tumour fixation into the exenteration specimen. This complex surgical procedure is not adequate for visceral pelvic side disease involving the larger sciatic foramen and for all forms of parietal pelvic side disease. Other criteria of patient selection for LEER include age <70 years, no significant comorbidity or mental illness, good performance status, a strong indication that local tumour control may have a chance to cure the patient or at least to prolong her life, and a high probability that the resection of the tumour with negative lateral surgical margins is achievable. Moreover, tumour size should be <5 cm, and the disease-free interval from irradiation should be >5 months. Höckel performed the LEER in 100 patients with recurrent or advanced gynaecological tumours, mainly represented by cervical cancer (n=63). Peri-operative mortality was 2%, major iatrogenic morbidity occurred in 70% of the patients, and the 5-year recurrence-free and disease-specific overall survival rates were 62 and 55%, respectively (68).

Lopez-Graniel *et al* (69) have suggested the use of 'neoadjuvant' pre-exenterative chemotherapy for patients with recurrent/persistent disease involving the pelvic wall, with the aim of shrinking the pelvic tumour and allowing a subsequent pelvic exenteration. These authors administered 2-6 (median, 4) cycles of platinum-based chemotherapy to 17 women with these characteristics. The 9 patients (53%) who responded to chemotherapy underwent pelvic exenteration and 4 of them obtained a pathological complete response. Major intra- or postoperative complications occurred in 55% of the patients and one woman died due to sepsis 4 months after surgery. The median survival was 11 months for the entire group, 32 months for the patients who underwent exenteration and 3 months for those who did not. It is noteworthy that the median survival of 11 months compares favourably with the median survival of 6-10 months reported in studies using systemic chemotherapy in the palliative setting (69-72). Further investigations and randomised controlled trials are needed to elucidate the therapeutic potential of this treatment modality.

### 5. Isolated para-aortic recurrence

The incidence of isolated para-aortic recurrence after definitive treatment of cervical cancer ranges from 2 to 12% (73-76). The prognosis of this relapse is usually poor, often being associated with a systemic spread of disease (74,75,77). Grisby *et al* reported that 20 women with this recurrence received external irradiation on the para-aortic lymph nodes and all died within 2 years (74). The median survival was related to the disease-free interval (7.5 months for the patients who failed within 2 years vs. 17.8 months for those who failed later; p=0.09) and to the irradiation dose (14.2 months for a dose >45 Gy vs. 7.1 months for a lower dose; p=0.004). However, according to recent data, concurrent chemo-radiation appears to yield a good clinical outcome especially in asymptomatic patients with an isolated para-aortic failure detected by CT or PET/CT (75-77). Chou *et al* (75) reported a 5-year overall survival of 51.2% for 14 women treated with concurrent chemo-radiation vs. 0% for the 5 women treated with irradiation alone or chemotherapy alone. Singh *et al* (76) reassessed the clinical reports of 14 cervical cancer patients with isolated para-aortic relapse. The 7 symptomatic patients, with one or more of the classic clinical findings of para-aortic recurrence (lower extremity oedema, sciatic pain and hydronephrosis) died of disease within 1.5 years of completing salvage therapy, whereas the 7 asymptomatic patients treated with irradiation (45-50.4 Gy) and concurrent cisplatin (40 mg/m$^2$/week) had a 5-year overall survival of 100% (p<0.01).

### 6. Distant recurrence or loco-regional recurrence not amenable by surgery or radiotherapy

The role of chemotherapy in this clinical setting is only palliative, and its administration is affected by several factors, such as decreased bone marrow function due to prior irradiation, limited drug distribution in previously irradiated tissues, and renal dysfunction due to ureteral obstruction (78).

Cisplatin is the most widely used drug, with a response rate of 17-38% and a median overall survival of 6.1-7.1 months (79-84). Potter *et al* (84) reported that chest metastases were more likely to respond to cisplatin than pelvic failures (73 vs. 21%, p=0.0007), although the site of relapse did not significantly affect survival. A Gynecologic Oncology Group (GOG) randomised trial compared 50 mg/m$^2$ of cisplatin vs. 100 mg/m$^2$ vs. 20 mg/m$^2$, days 1-5 every 3 weeks in 497 patients (80). The response rates were 20.7, 31.4 and 25.0%, respectively, the median progression-free interval ranged from 3.7 to 4.6 months and the median overall survival ranged from 6.1 to 7.1 months. Cisplatin at 100 mg/m$^2$ single dose achieved a higher response rate than cisplatin at a dose of 50 mg/m$^2$ (p=0.015), without any improvement in the clinical outcome and with a greater haematological toxicity and nephrotoxicity. Therefore, 50 mg/m$^2$ is the recommended dose of cisplatin.

Phase II studies with single agents have shown the following response rates: 15-28% for carboplatin (400 mg/m$^2$ every 4 weeks) (85-87); 11-33% for ifosfamide (5 g/m$^2$, 24-h infusion every 3 weeks or 1.2-1.5 g/m$^2$, days 1-5 every 4 weeks) (88-90); 30% for vindesine (2 mg/m$^2$ on two subsequent days/week) (91); 7-18% for vinorelbine (30 mg/m$^2$/week or 30 mg/m$^2$, days 1 and 8 every 3 weeks) (92-94); 4.5-8% for gemcitabine (800 mg/m$^2$, days 1, 8 and 15 every 4 weeks) (95,96); 15-31% for paclitaxel (110-250 mg/m$^2$ every 3 weeks) (97-100); 9% for docetaxel (100 mg/m$^2$ every 3 weeks) (101); 13-19% for topotecan (1.5 mg/m$^2$, days 1-5 every 3 weeks) (102,103); 16-21% for irinotecan (125 mg/m$^2$/week for 4 weeks every 6 weeks or 350 mg/m$^2$ every 3 weeks) (104,105); and 15-18% for pemetrexed (500-900 mg/m$^2$ every 3 weeks) (106-108). Higher response rates have been reported for lesions in previously unirradiated areas compared with those in irradiated fields. The median overall survival ranged from 4.9 to 11 months, with a median value of 7 months (107).

Combination chemotherapy should include drugs that have demonstrated single-agent activity, non-overlapping toxicity and additive or synergistic activity with no significant increase in toxicity. Phase II-III studies have shown the following response rates: 22-68% for the combination of cisplatin (50-100 mg/m$^2$) + 5-fluorouracil (1000 mg/m$^2$, days 1-5) (109-111); 50% for cisplatin (50 mg/m$^2$) + capecetabine (1,000 mg/m$^2$, days 1-14, twice daily) (112); 54% for cisplatin (120 mg/m$^2$) + bleomycin (10 mg/m$^2$, day 1 bolus + 10 mg/m$^2$, days 5-7, continuous infusion) (113); 38-50% for cisplatin (20 mg/m$^2$, days 1-5 or 50 mg/m$^2$, day 1) + ifosfamide (1.5-2.5 g/m$^2$, days 1-5) (114,115); 41-64% for cisplatin (50 mg/m$^2$) + gemcitabine (1250 mg/m$^2$, days 1 and 8) (116); 59-78% for cisplatin (60 mg/m$^2$) + irinotecan (60 mg/m$^2$, days 1, 8 and 15) (117,118); and 45-47% for cisplatin (75 mg/m$^2$) + paclitaxel (135-175 mg/m$^2$) (119-121). These trials have shown an advantage in response rates for cisplatin-based combination regimens when compared with single-agent cisplatin, without any benefit in terms of survival.

A GOG study randomly allocated 294 patients with stage IVb or recurrent or persistent cervical cancer to receive either cisplatin (50 mg/m$^2$) or topotecan (0.75 mg/m$^2$, days 1-3) + cisplatin (50 mg/m$^2$, day 1, every 3 weeks) (122). Combination chemotherapy obtained a higher response rate (27 vs. 13%; p=0.004), a longer median progression-free survival (4.6 vs. 2.9 months; p=0.014) and a longer median overall survival (9.4 vs. 6.5 months; p=0.017), associated with a more frequent grade 3-4 haematological toxicity. This is the first randomised phase III trial demonstrating a survival advantage for combination chemotherapy vs. single-agent cisplatin.

The GOG trial 204 compared the doublets of cisplatin (50 mg/m$^2$, day 2) + paclitaxel (135 mg/m$^2$, 24-h infusion), cisplatin (50 mg/m$^2$, day 1) + vinorelbine (30 mg/m$^2$, days 1 and 8), and cisplatin (50 mg/m$^2$, day 1) + gemcitabine (1000 mg/m$^2$, days 1 and 8) vs. the combination of cisplatin (50 mg/m$^2$, day 1) + topotecan (0.75 mg/m$^2$, days 1-3) every 3 weeks (123,124). There was no significant difference in survival among the different arms, with a trend in favour of a cisplatin + paclitaxel regimen that was also associated with a better quality of life.

Cisplatin-based three- or four-drug regimens have achieved no clear advantage vs. cisplatin-containing doublets or single-agent cisplatin in terms of clinical outcome in patients with persistent or recurrent cervical cancer (125-130). The combination of ifosfamide (5 g/m$^2$, 24-h infusion) + paclitaxel (175 mg/m$^2$) + cisplatin (75 mg/m$^2$) (TIP regimen) obtained a significantly higher pathological optimal response rate when compared with the combination of ifosfamide (5 g/m$^2$, 24-h infusion) + cisplatin (75 mg/m$^2$) in patients with

locally advanced squamous cell cervical cancer undergoing neoadjuvant chemotherapy followed by radical hysterectomy (131). However, three phase II trials have reported response rates of 46-67% for TIP in patients with recurrent or persistent disease, similar to those obtained with cisplatin-containing doublets (127-129).

Resection of isolated metastases can sometimes represent a reasonable option in accurately selected patients, particularly in those with solitary inguinal or lung metastases (132,133).

Molecularly -targeted therapy will hopefully offer new treatment options for patients with advanced, persistent or recurrent cervical cancer. In a phase II GOG trial, bevacizumab (15 mg/kg) was administered every 3 weeks to 46 women with persistent or recurrent disease (134). Eleven patients (24%) survived progression-free for at least 6 months, and 5 patients (11%) had partial responses. The GOG has recently designed a bifactorial-randomized trial introducing for the first time a non-platinum doublet (paclitaxel + topotecan) and bevacizumab compared with cisplatin + paclitaxel (135).

Bellone *et al* found that 14 out of 14 (100%) primary cervical cancer cell lines from cervical biopsies and recurrent sites of disease, as well as 7 out of 8 (87.5%) established cervical cancer cell lines expressed epidermal growth factor receptor-1 (136). Minimal complement-dependent cytotoxicity was detected in the majority of cell lines exposed to complement ± cetuximab in the absence of peripheral blood lymphocytes. In contrast, cell lines were highly sensitive to cetuximab-mediated antibody-dependent cellular cytotoxicity when challenged with peripheral blood lymphocytes from either healthy donors or cervical cancer patients. Gefitinib obtained no objective response but achieved a stabilization of disease in 20% out of 30 patients with recurrent cervical cancer resistant to standard treatment (137). Two GOG trials [GOG-227E (cetuximab) and GOG-76D (cetuximab + cisplatin)] are currently assessing the role of cetuximab in recurrent or metastatic cervical cancer (138).

## 7. Conclusions

Recurrent cervical cancer is a difficult challenge for gynecologic oncologists. Patients with central or lateral pelvic failure after surgery alone can be treated with concurrent cisplatin-based chemo-radiation, whereas pelvic exenteration usually represents the only therapeutic option with curative intent for women with central pelvic relapse after irradiation. Concurrent cisplatin-based chemo-radiation is the treatment of choice for isolated para-aortic lymph node recurrence, with satisfactory chances of a cure in asymptomatic patients. Chemotherapy is administered with palliative intent to patients with distant or loco-regional failures not amenable by surgery or irradiation. Cisplatin-based combination chemotherapy increases response rates when compared with single-agent cisplatin, but median overall survival is usually shorter than one year. However some cases of unexpected long-term disease-free survival after salvage chemotherapy have been reported in the literature (139,140). In a GOG phase III trial the combination topotecan + cisplatin obtained a significantly longer progression-free survival and overall survival when compared with single-agent cisplatin in patients with metastatic or recurrent or persistent cervical cancer. A subsequent GOG study has shown a trend in terms of longer overall survival and better quality of life for the doublet cisplatin + paclitaxel vs. the doublets cisplatin + topotecan, cisplatin + vinorelbine and cisplatin + gemcitabine. Molecular-targeted therapy may represent a novel therapeutic tool, but its use alone or in combination with chemotherapy is still investigational.

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