Review Article

Management of recurrent cervical cancer. Review of the literature and case report

Ph. Elst, *M.D.*; **F. Ahankour,** *M.D.*; **W. Tjalma,** *M.D., Ph.D.*

Department of Gynecology and Gynecological Oncology, University Hospital Antwerp, Edegem (Belgium)

Summary

The purpose of this study is to report the use of a gemcitabine-vinorelbine-cisplatin (GVP) regimen as a successful treatment for a patient with recurrent squamous cervical cancer. The patient was initially diagnosed with a Stage IIb squamous carcinoma of the uterine cervix. A radical hysterectomy with pelvic lymphadenectomy was performed. Adjuvant radiotherapy was given. Eighteen years later, a pelvic recurrence with involvement of the pelvic sidewall was diagnosed and treated with the combination of GVP. A complete clinical and radiological response was achieved and a complete pathological response was confirmed afterwards. Currently, 67 months later, the patient is well and there are no signs of disease.

We reviewed the literature concerning the staging and the chemotherapeutical and surgical treatment of recurrent cervical. Based on the recent literature, we conclude that pelvic examination, MRI, PET/CT and laparoscopy are essential in staging recurrent disease, and that laterally extended endopelvic resection (LEER) as well as pre-exenterative chemotherapy are promising novel therapeutic modalities for recurrent cervical cancer with pelvic extension in an irradiated area. In order to make recent data more transparant and practical we designed a classification and flow-chart for the management of recurrent cervical cancer.

Key words: Operable breast cancer; Primary chemotherapy.

Introduction

Cancer of the cervix is the leading cause of cancer death in women worldwide, with a mortality rate of about 50% [1]. Invasive squamous cell carcinoma is the most common variety of invasive cancer of the cervix (± 80%). Complications of persistent or recurrent tumor in the pelvis are the main cause of death.

The majority of early-stage tumors (FIGO IA/IB/IIA) are treated by radical surgery. There is now evidence that adjuvant chemoradiation improves local control and survival in patients with early clinical stages exhibiting histopathological risk factors treated with standard radical hysterectomy [2]. Approximately half of the patients treated surgically will also receive chemoradiotherapy and thus the majority of patients have been irradiated when their treatment is terminated.

Advanced stages are now treated by concurrent chemoradiation as the standard of care.

Nevertheless, a small proportion of patients will develop a relapse.

The management of patients with recurrent cervical cancer is a therapeutic challenge and depends on the mode of primary treatment and the location of recurrence.

Patients who have been treated initially with surgery (without postoperative radiation) should be considered for concomittant chemoradiation therapy, and those who have had (chemo)radiation should be considered for surgical treatment. Local recurrence in an irradiated pelvis indicates a very dismal prognosis.

Revised manuscript accepted for publication April 5, 2007

Up to now, surgical therapy for postirradiation recurrence was limited to patients with central pelvic disease. They underwent pelvic exenteration, en bloc resection of the bladder, genital tract, and rectum, first described by Brunschwig in 1948 [3].

Extension of the tumor to the pelvic sidewall, the most common situation of local failure, is a contraindication to exenteration; these patients are no longer regarded eligible for curative therapy.

Chemotherapy is tradionally considered palliative only and is reserved for patients who are not considered curable by the other two modalities.

Case Report

At the age of 34, in 1982, the patient was diagnosed with squamous carcinoma of the cervix clinically Stage IIb with the main involvement of the anterior lip and suspicion of a small extension into the right fornix and parametrium.

Due to heavy vaginal bleeding, external radiation was given for 12 days (total of 19 Gy). External irradiation was followed by a caesium insertion when 55 mg in a uterine tube and 20 mg in each of two small vaginal packets were inserted for 26 hours.

Subsequently, radical hysterectomy (Wertheim) with pelvic lymphadenectomy was performed. Pathological examination showed that every margin was free of tumor. One of the six lymph nodes removed from the left external iliaca artery showed a focus of mainly keratinized squamous cell carcinoma in which the cellular structure was indistinct and viability was doubtful. One of the two lymph nodes removed from the right external iliacal artery showed small foci of squamous cell carcinoma, the cells of which showed some irradiation changes.

The other pelvic lymph nodes were free of tumor. Adjuvant radiotherapy was given, 30 Gy in 20 fractions for four weeks.

Eighteen years later, in 2000, the patient consulted for vaginal discharge. On clinical examination a mass was seen on the left vaginal wall. The tumor infiltrated the vaginal top and the lower one-third of the recto-vaginal septum, and there seemed to be infiltration of the left pelvic sidewall.

Pelvic computed tomography (CT) showed an asymmetrically thickened vaginal cuff. Magnetic resonance imaging (MRI) of the pelvis showed a nodular asymmetric structure on the vaginal cuff. There was no clear free margin with the posterior bladder wall. There were no enlarged pelvic lymph nodes nor signs of metastatic disease.

Subsequently the performed biopsy revealed a well differentiated invasive squamous cell carcinoma in the vagina.

Infiltration of the left pelvic sidewall is a contraindication for pelvic exenteration; the prior radiation excluded a third session of radiation. The best option for treatment seemed chemotherapy.

The patient was recruited for a phase I study of the combination of gemcitabine, vinorelbine and cisplatin (GVP). The dose of gemcitabine was 1000 mg/m^2, of vinorelbine 25 mg/m^2 and cysplatinum 75 mg/m^2. Cisplatin was given on day 1 and gemcitabine and vinorelbine were administered on days 1 and 8, every 21 days. The patient received gemcitabine four hours before vinorelbine and cisplatin. Gemcitabine was given in a 30-minute intravenous infusion, vinorelbine over ten minutes and cisplatin over one hour.

The treatment was tolerated relatively well and was only complicated by mild neutropenia which caused a delay of one week before starting the third cycle.

After four cycles there was a radiological (MRI) and clinical complete response. The patient had received a total of six cycles when we performed a clinical examination, cystoscopy and rectoscopy under general anesthesia, all of which showed no tumor, followed by second-look laparatomy. No tumor was seen, multiple biopsies were taken, including of the vaginal vault, and paraaortal lymph node sampling was performed. Cytology and histology showed acute inflammation but no malignancy. The conclusion was that she had a complete pathological response.

At present, 67 months later, there are no signs of disease.

Discussion

A literature review concerning the diagnostic approach, staging and chemotherapeutical and surgical treatment of recurrent cervical cancer was done. The present manuscript proposes a classification and flow-chart for the management of recurrent cervical cancer.

Diagnosis and staging

First, as in the assesment of primary disease, the diagnosis of recurrent cervical cancer has to be established. Most of the time, this can be done by a gynecological clinical examination with inspection, palpation and biopsy of the recurrent tumor. The consequences of this diagnosis are huge and the morbidity of every treatment modality applied after this diagnosis is high, thus histological confirmation is mandatory. A biopsy with or without guidance is often possible in the office; laparoscopic evaluation with biopsy may be necessary.

Step two is to define the extent of the disease. Cancer recurrence with metastasis outside the pelvis is considered uncurable. A systematic search for clinical, biochemical or radiological arguments for metastatic disease has to be performed.

Physical examination focuses on looking for signs of cachexia, palpable supraclavicular or inguinal adenopathy, hepatomegaly or intraabdominal masses. Palpable nodes almost always represent metastatic disease and therefore should be biopsied or aspirated (FNAC).

Relevant biochemical data are HIV status, liver enzymes, complete blood count, platelet count, glucose, electrolytes and renal function tests.

Staging the primary disease is commonly done by a normal radiograph or CT scanning of the chest and a CT or MRI of the abdomen and pelvis. However, since salvage therapy often causes high morbidity and even mortality, treatment of patients with unrecognized metastatic disease should be avoided at all costs. Recently, the PET/CT has been regarded as the first choice in this high-risk population. In a review of published series examining the utility of imaging studies in women with all stages of cervical cancer and either histological confirmation of node status or clinical follow-up of more than six months, the pooled sensitivity and specificty of PET/CT, CT and MRI for pelvic nodal involvement in newly diagnosed cervical cancer were: PET (sensitivity: 79%, specificity: 99%), MRI (sensitivity: 72%, specificity: 96%) and CT (sensitivity: 47%, specificity not determined) and for paraaortic node metastasis, PET had a sensitivity of 84%, and a specificity of 95% [4] (Table 1).

Table 1. — *Sensitivity and specificity of CT, MRI and PET for pelvic nodal involvement in newly diagnosed cervical cancer [4].*

	Sensitivity (%)	Specificity (%)
CT	47	–
MRI	72	96
PET	79	99

CT: Computed Tomography; MRI: Magnetic Resonance Imaging, PET: Positron Emission Tomography.

In a study of 101 women undergoing radiotherapy and chemotherapy for clinically staged cervical cancer (predominantly Stage IB2 to III) two-year progression-free survival rates, based solely on paraaortic lymph node status, were 64, 18 and 14% for those with CT/PET-negative, CT-negative/PET-positive, and CT/PET-positive disease, respectively. In multivariate analyses, PET-positive paraaortic lymph node status was the only significant variable predicting lower progression-free survival [5]. The high specificity of PET/CT makes aspiration or biopsy of a positive lymph node unnecessary.

Bone scans are not indicated unless the woman gives a history of recent onset of bone pain.

Only if there is central pelvic disease is there an indication for exenteration. Pelvic examination is inaccurate in differentiating the recurrent tumor, post-radiation fibrosis and endometriosis. Therefore, post-radiation fixation to the sidewall on clinical examination may not be a contraindication for further curative treatment. Moreover, absence of fatty planes lateral to the tumor on CT nor MRI should be used for determining resectability. False-positive results for pelvic sidewall extension as well as false-negative results have been reported [6-8].

Despite the fact that dynamic contrast-enhanced subtraction MRI may differentiate between recurrent tumor and benign conditions, its accuracy in determining surgical eligibility for pelvic exenteration has been estimated as 83% [9]. This explains why despite thorough preoperative investigation, inoperable disease is discovered at the time of laparotomy in up to 50% of cases [10]. This has led to propose laparoscopy to select candidates to undergo the procedure, which proved to be effective as it may spare laparotomy in half of the patients [11, 12].

Chemotherapy

Chemotherapeutical treatment of recurrent cervical cancer is considered a major challenge. There are two important reasons for this.

First, many patients will have had prior radiation therapy. This is known to reduce response rates by at least 50%. One hypothesis to explain this fact is that radiation may select out not only radiation-resistant cells, but also drug-resistant cells. Moreover, radiation-induced damage of blood vessels may cause lower perfusion of the recurrent tumor. This has two possible consequences:

1) a reduced concentration of the cytotxic drugs within the tumor, and

2) less proliferation of the cancer cells, and therefore a reduction of the anti-proliferative effects of chemotherapeutical agents.

Second, pelvic radiation causes fibrosis, which makes clinical and radiological evaluation of the response difficult.

Although several agents have been investigated in the treatment of advanced or recurrent cervical cancer, as a single-agent or in combination with other agents, results are generally poor and only a small percentage of complete response has been noted [13-20].

Single-agent chemotherapy

The response rates of the more active single agents vary between 15% and 34%. Cisplatin remains the most extensively studied and the most active single agent, with a response rate of 23%. It acts principally by attacking and damaging DNA structure.

Table 2. — *Response of different single-agent chemotherapy regimens used for cervical cancer. From: Morris M. et al. [13]. Wagenaar H.C. et al. [20].*

	Drug response	Trial size	Response rate %
Cyclophosphamide	38	251	15
Ifosfamide	35	157	22
Carboplatin	27	175	15
Doxorubicin	45	266	17
5-fluorouracil	29	142	20
Methotrexate	17	96	18
Vincristine	10	55	18
Irinotecan	36	192	19
Topotecan	8	43	19
Paclitaxel	14	74	19
Docetaxel	12	35	34
Cisplatin	190	815	23
Vinorelbine	13	74	18

There is no evidence of a survival improvement with cisplatin alone.

Table 2 summarizes the reported responses of the most studied single-agent chemotherapy regimens.

Vinorelbine is a vinca derivative and exerts its biological effect by inhibiting microtubule assembly. Morris *et al.* studied the activity of vinorelbine as a single agent in patients with advanced or recurrent carcinoma of the cervix and found an 18% response rate [13]. Another phase II trial of Lhommé and Vermorken *et al.* found a response rate of 17% while 20% had stable disease. They concluded that vinorelbine has a moderate activity in recurrent or metastic cervical cancer with only mild neurotoxicity [14].

Gemcitabine as a single agent, in contrast, has demonstrated only minimal anti-tumor activity in previously treated patients with squamous cell cancer of the uterine cervix: Shilder *et al.* found only one partial response in a total of 19 patients. They concluded that since gemcitabine is known to potentiate the cytotoxicity of cisplatin and radiotherapy, further development of gemcitabine would only be indicated in combination with these treatment modalities [15].

Combination chemotherapy

Cisplatin-based combination therapy has been reported to yield higher response rates than cisplatin single-agent therapy, although this is achieved at the cost of significantly higher hematologic and nonhematologic toxicity. A number of drug combinations have been evaluated, but there have been few randomized controlled trials comparing combinations either with single agents or with two or three drug combinations [16-20]. With the increasing number of drugs, the toxicity of these regimens may become a problem, with myelosuppression and nephrotoxicity being the main side-effects [16].

For three decades the Gynecologic Oncology Group (GOG) has been without equal in its sustained clinical development of systemic chemotherapy for cervical cancer. In a review of these studies, Moore concludes that both paclitaxel and topotecan, in combination with cisplatin, have yielded superior response rates and progression-free survival without diminishing patient-reported quality of life [16]. However, improved overall survival has only been established with cisplatin plus topotecan and median survival is less than one year with these cisplatin-containing combinations. Most patients do not respond to treatment and are thus subjected to treatment-related toxicity without a meaningful benefit (Table 3).

Table 3. — *Combination Chemotherapy: Survival rates for the three Gynecologic Oncology Group protocols (110, 169 and 179).*

Protocol	Regimen	No. of patients	OR (%)	CR (%)	PFS	OS
GOG 110	P	140	19	6	3.2	8.0
	P+IFX	151	31	13	4.6	8.3
GOG 169	P	134	19	6	3.0	8.9
	P+ TAX	130	36	15	4.9	9.9
GOG 179	P	145	13	3	2.9	7.0
	P+TOPO	148	26	10	4.6	9.2

OR: Odds ratio; CR: Complete response; PFS: Progression-free survival; OS: Overall survival; P: Cisplatin; IFX: Ifosfamide; TAX: paclitaxel; TOPO: Topotecan; PFS and OS: in months [16].

In a review by Brader *et al.* in 1998 on the results of 190 advanced or recurrent disease patients treated with 14 different chemotherapy protocols, the overall response rate was 20.0% (4.2% complete response; 15.8% partial response), with a median response duration of 4.8 months [17].

In a phase II study by Pignata *et al.* of cisplatin and vinorelbine as first-line chemotherapy in patients with carcinoma of the uterine cervix, including advanced and recurrent disease, three complete responses and four partial responses of a total of 15 patients in the subgroup of patients with recurrent disease (overall rate of 46.7%) were described [18]. In this subgroup, responses were observed either in patients with extrapelvic (one complete and one partial response of four patients) and with pelvic recurrence (two complete responses and three partial responses of 11 patients). Importantly, in this latter subgroup with pelvic recurrence, as in our case report, only three patients had received prior radiotherapy of the pelvis. For these patients, they recorded two cases of progressive disease and one partial response.

Similarly, in a study by Gebbia *et al.* of vinorelbine and cisplatin for the treatment of recurrent and metastatic disease of the uterine cervix, patients with recurrent disease within the previous radiation field showed a 28% overall response rate with no complete response [19].

Although complete response after adjuvant chemotherapy (after surgery, radiotherapy or both) during the initial therapy has been described [20], complete response in a previously irradiated field after chemotherapy in general is very rare.

Recurrence in a previously irradiated field is a well known negative prognostic factor for chemotherapeutical response and overall survival, and is even a proven sigificant independent prognostic factor for a shorter time to progression after recurrence [21]. On the other hand, there are two known positive prognostic factors in our case report that could have contributed to the described complete response and/or the disease-free survival of at least six years.

First, the squamous tumor cells were well differentiated. Second, the very long disease-free survival of 18 years after the initial diagnosis is known to be associated to response to chemotherapy. Moreover, those with a longer disease-free interval from initial diagnosis to first recurence and response to chemotherapy are known to have a longer survival duration after relapse [21]. It is possible, however, that the presenting tumor 18 years after primary treatment was in fact a second, primary vaginal carcinoma.

Efficacy of local and systemic therapy can be increased by combining radiotherapy and/or chemotherapy with locoregional hyperthermia (LRH). Increasing the temperature of the target tissue up to 41-43°C leads to local hyperemia and the tumor tissue becomes more responsive to cytotoxic interventions. Despite the fact, that the available data are still preliminary, the inclusion of LRH into multimodal cancer therapy concepts appears to be very promising. Well-designed comparative studies are still needed to evaluate the role of hyperthermia as an adjunct to conventional cancer therapy.

To conclude this section, it is important to realize that complete response to chemotherapy of recurrent cervical cancer is rare, especially in a priorly radiated field. Therefore, the use of toxic and expensive combinations, especially in a palliative setting, should be well balanced against potential hazards.

Surgery

As mentioned in our introduction, recurrent cervical cancer traditionally is treated by

– chemoradiation if the primary disease was treated by surgery only,

– palliative chemotherapy if the primary disease was treated by chemoradiation and if the recurrent tumor is considered irresectable, or

– pelvic exenteration.

Pelvic exenteration involves the en bloc removal of the bladder, genital tract and rectum. It is commonly reserved for a small subgroup (10%) of patients with small and central recurrent tumors. However, most pelvic recurrences do show a diffuse growth pattern with involvement of one or both pelvic sidewalls. Because of this, most patients are left with no curative options. Therefore, it is important that other therapeutic modalities are investigated for these women. Since 2000, three novel therapeutic modalities have been proposed.

First, high-dose-rate intraoperative radiation therapy (HDR-IOR) seems to broaden the selection of operable cases [22]. However, it has two main disadvantages: only the patients who had complete macroscopic resection after surgery appeared to benefit from HDR-IOR [23] and this form of radiation is also not widely available.

Second, Hockel proposed the promising laterally extended endopelvic resection (LEER), as a novel surgical treatment of locally recurrent cervical cancer involving the pelvic sidewall. He extended the lateral resection plane of the pelvic exenteration to the medial aspects of the lumbosaral plexus, sacrospinous ligament, acetabulum and obturator membrane [24]. By doing so, he could obtain tumor-free margins in 34 of 36 patients with advanced but mainly recurrent cervical cancer with pelvic involvement. Five-year survival probability was 46% in those patients who were considered only for palliation with current treatment. Most patients without evidence of disease at least two years after LEER achieved a good quality of life. However, postoperative complications occurred in almost half of the patients and there was one treatment-related death. Moreover, not every recurrent tumor with pelvic sidewall involvement can be approached by this procedure, as it is limited to tumors smaller than 5 cm that do not involve the large sciatic foramen nor the parietal pelvic sidewall, with a recurrence-free interval of more than five months after primary radiation therapy. The high morbidity, the highly complicated technique, and the fact that it is only indicated for a selected subgroup of patients are important disadvantages of LEER [25].

Third, Lopez-Graniel *et al.* have proposed neo-adjuvant chemotherapy prior to exenteration in cases of initially non-operable persistent or recurrent cervical cancer. This so called pre-exenterative chemotherapy is given under the rationale that shrinking the tumor would allow its resection. In this study nine of the 17 patients could undergo pelvic exenteration after chemotherapy; eight had tumor-free margins. The median survival for the whole group was 11 months, three months for the non-operated group and 32 months for those subjected to exenteration [26]. A main problem is, that, despite a thorough preoperative investigation, inoperable disease was discovered at the time of laparotomy in 50% of the cases. Laparoscopy with or without sentinel node biopsy, may be helpful in avoiding unnecessary laparotomy.

Management of recurrent cervical cancer

The following proposal of management of patients with recurrent cervical cancer is solely disease-based and does not integrate patient characterics (cf. flow-chart). It is clear however, that the latter are critical in making choices in the management of these high-risk patients with occasionally important comorbidity.

The choice of the modality of primary treatment of cervical cancer is determined by FIGO staging, which is a clinical staging system. Stage IA2, IB1 and IIA are commonly treated by radical hysterectomy and lymphadenectomy. Treating Stage IIB and higher by chemoradiation is the actual standard of care. There is some controversey about the treatment of Stage IB2: the majority treat these patients by chemoradiation, while some still perform a radical hysterectomy. Whatever the primary treatment, intensive follow-up by a gynecologist is mandatory, especially the first five years after primary treatment, as most recurrent tumors present during the first two years after the initial treatment.

If the histological diagnosis has been established, the extent of the disease has to be confirmed. Of course, a general physical and gynecological examination with a pelvic examination should be performed. Fine needle aspiration cytology of palpable nodes should be done and biochemical data should be collected. Integrated PET/CT is probably the most sensitive test for extrapelvic metastasis and should be the first choice.

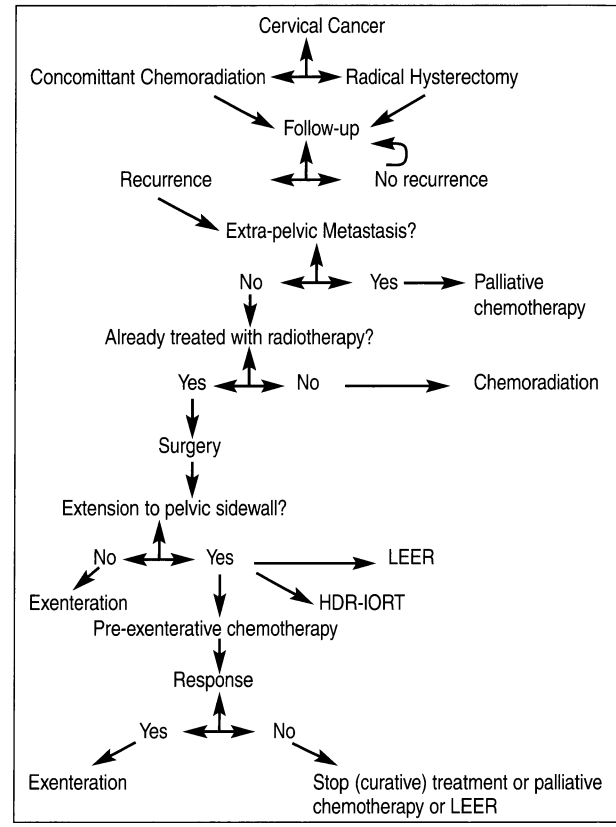
Clearly, if extrapelvic metastasized disease is found, palliative chemotherapy should be considered.

In the management of patients with pelvic recurrence of cervical cancer, the next question that should be asked is: 'has the patient already been treated with radiotherapy?'. If this is not the case, principally she should be given radiotherapy. If this is the case however, her prognosis becomes much worse and the left-over treatment alternatives are known to have more morbidity and even mortality, and less effectivity.

The first step in the management of non-metastasized recurrent cervical cancer that has already been treated with radiotherapy is to exclude pelvic sidewall involvement.

To exclude pelvic extension, a pelvic examination and (dynamic contrast-enhanced subtraction-)MRI should be done. As already mentioned, they are both very inaccurate tests to predict pelvic extension. Therefore, diagnostic laparoscopy with or without a sentinel node biopsy, must seriously be considered. The laparoscopy should be done by a surgeon trained in pelvic surgery to evaluate the surgical eligibility for a pelvic exenteration. An exenteration, if possible, can be performed simultaneously but preferrably, for practical reasons, it should be done at two different times.

Disease-based flow-chart for management of recurrent cervical cancer



If pelvic extension has been demonstrated by laparoscopy, the recent literature suggests three therapeutic alternatives. HDR-IORT, however, is not widely available and its independent effectivity has yet to be proven. LEER, on the other hand, seems promising, but has a high morbidity, demands great expertise in pelvic surgery and is only appropiate for a subgroup of patients with recurrent cervical cancer. Therefore, exenterative surgery seems to be first choice for most patients.

Gynecological examination, MRI and PET/CT should be used to evaluate the response of the tumor to the chemotherapeutical agents. Combination chemotherapy probably should, whenever possible, be preferred to single-agent chemotherapy in this selected population. After chemotherapy, a 'second-look laparoscopy' should be considered to reevaluate surgical eligibility, even if no radiological response has been demonstrated, as actual response may be greater than seen on CT or MRI. If no

response or insufficient response has been established, palliative chemotherapy with (an) alternative agent(s) yet can be considered.

Based on this approach of the management of recurrent cervical cancer, a classification of recurrent cervical cancer has been designed (Table 4). Patients with recurrent cervical cancer can be classified in four categories by means of pelvic examination, MRI, PET/CT and laparoscopy. These four well-defined categories have both prognostic as well as therapeutic relevance, as the most important prognostic variables (extra-pelvic metastasis, prior radiotherapy, pelvic extension, time of recurrence after first treatment and size of tumor) are integrated (the higher the number of the category, the worse the prognosis) and each category is associated with a specific optimal choice of treatment.

Table 4. — *Classification of recurrent cervical cancer.*

Category	Definition	Treatment
I	No previous radiotherapy or pelvic disease	Chemoradiation
II	Previous radiotherapy and central pelvic disease	Exenteration
III	Previous radiotherapy and pelvic extension	
A)	Recurrence > 5 months after radiotherapy	
1	Tumor < 5 cm	Pre-exenterative chemotherapy ± exenteration or LEER
2	Tumor > 5 cm (or involvement of the larger sciatic foramen or parietal pelvic sidewall disease	Pre-exenterative chemotherapy ± exenteration
B)	Recurrence < 5 months after radiotherapy	
IV	Extrapelvic metastasis	Palliative chemotherapy

The first category (category I) includes the patients who only have pelvic disease and who have not yet been treated by radiotherapy; they can now be treated by radiotherapy.

The second category (category II) is defined by central pelvic disease and prior radiotherapy; these patients should be treated by pelvic exenteration.

The third category (category III) is defined by pelvic extension and prior radiotherapy and has several subcategories: if the disease-free survival is longer than five months (category IIIA), there are two other subgroups; the patients with a tumor smaller than 5 cm (category IIIA1), can be treated by LEER or pre-exenterative chemotherapy, followed by exenteration in case of sufficient response; if the tumor is bigger than 5 cm (category IIIA2) (or in case of other contraindications for LEER: involvement of the larger sciatic foramen or of the parietal pelvic sidewall) or if the recurrence presents before five months after radiotherapy, it can be treated curatively by pre-exenterative chemotherapy and exenteration only. In case of extrapelvic cisease (category IV), only palliative chemotherapy can be considered.

Conclusion

Treatment of recurrent cervical cancer with pelvic extension in a previously irradiated field is a huge therapeutic challenge and, until recently, was considered incurable.

Pelvic examination, MRI, PET/CT and laparoscopy are, based on available data, the first choice to stage recurrent cervical cancer. We designed a classification of recurrent cervical cancer with prognostic and therapeutic relevance.

Although chemotherapy was traditionally considered palliative only, we report a complete response after a gemcitabine-vinorelbine-cisplatin regimen for recurrent squamous carcinoma of the uterine cervix with long-term disease-free survival. This supports the pre-exenterative chemotherapy approach. Laterally extended endopelvic resection (LEER) also seems promising. These novel therapeutic approaches of recurrent cervical cancer should stimulate a more systematic and therapeutic approach to these patients.

References

[1] Jemal A., Siegel R., Ward E. *et al.*: "Cancer statistics, 2006". *CA Cancer J. Clin.*, 2006, *56*, 106.

[2] Sedlis A., Bundy B.N., Rotman M.Z., Lentz S.S., Muderspach L.I., Zaino R.J: "A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy. A Gynaecologic Oncology Group study". *Gynecol. Oncol.*, 1999, *73*, 177.

[3] Brunschwig A.: "Complete excision of pelvic viscera for advanced carcinoma". *Cancer*, 1948, *1*, 177.

[4] Havrilesky L.J., Kulasingam S.L., Matchar D.B., Myers E.R: "FDG-PET for management of cervical and ovarian cancer". *Gynecol. Oncol.*, 2005, *97*, 183.

[5] Grigsby P.W., Siegel B.A., Dehdashti F.: "Lymph node staging by positron emission tomography in patients with carcinoma of the cervix". *J. Clin. Oncol.*, 2001, *19*, 3745.

[6] Halpin T.F., Frick H.C., Munnell E.W.: "Critical points of failure in the therapy of cancer of the cervix: a reappraisal". *Am. J. Obstet. Gynecol.*, 1972, *114*, 755.

[7] Walsh J.W., Amendola M.A., Hall D.J., Tisnado J., Goplerud D.R.: "Recurrent carcinoma of the cervix: CT diagnosis". *Am. J. Roentgenol.*, 1981, *136*, 117.

[8] Jeong Y.Y., Kang H.K., Chung T.W., Seo J.J., Park J.G.: "Uterine cervical carcinoma after therapy: CT and MR imaging findings". *Radiographics*, 2003, *23*, 969.

[9] Popovich M.J., Hricak H., Sugimura K., Stern J.L.: "The role of MR imaging in determining surgical elegibility for pelvic exenteration". *Am. J. Roentgenol.*, 1993, *160*, 525.

[10] Haas T., Buchsbaum H.J., Lifshitz S.: "Nonresectable recurrent pelvic neoplasm. Outcome in patients explored for pelvic exenteration". *Gynecol. Oncol.*, 1980, *9*, 177.

[11] Zeisler H., Joura E.A., Moeschl P., Maier U., Koelbl H.: "Preoperative evaluation of tumor extension in patients with recurrent cervical cancer". *Acta Obstet. Gynecol. Scand.*, 1997, *76*, 474.

[12] Kohler C., Tozzi R., Possover M., Schneider A.: "Explorative laparoscopy prior to exenterative surgery". *Gynecol. Oncol.*, 2002, *86*, 311.

[13] Morris M., Brader K.R., Levenback C., Burke T.W., Atkinson E.N., Scott W.R., Gerhenson D.M.: "Phase II study of vinorelbine in advanced and recurrent squamous cell carcinoma of the cervix". *J. Clin. Oncol.*, 1998, *16*, 1094.

[14] Lhommé C., Vermorken J.B., Mickiewicz E., Chevalier B., Alvarez A., Mendiola C. *et al.*: "Phase II trial of vinorebine in patients with advanced and/or recurrent cervical carcinoma: an EORTC Gynaecological Cancer Cooperative Group Study". *Eur. J. Cancer*, 2000, *36*, 194.

[15] Schilder R.J., Blessing J.A., Morgan M., Mangan C.E., Rader J.S.: "Evaluation of gemcitabine in patients with squamous cell carcinoma of the cervix: a phase II study of the gynaecologic oncology group". *Gynecol. Oncol.,* 2000, *76,* 204.
[16] Moore D.: "Chemotherapy for recurrent cervical carcinoma". *Curr. Opin. Oncol.,* 2006, *18,* 516.
[17] Brader K.R., Morris M., Levenback C., Levy L., Lucas K. R., Gershenson D.M.: "Chemotherapy for cervical carcinoma: Factors determining response and implications for clinical trial design". *J. Clin. Oncol.*, 1998, *16,* 1879.
[18] Pignata S., Silvestro G., Ferrari E., Selvaggi L., Perrone F., Maffeo A. *et al.*: "Phase II study of cisplatin and vinorelbine as first-line chemotherapy in patients with carcinoma of the uterine cervix". *J. Clin. Oncol.,* 1999, *17,* 756.
[19] Gebbia V., Caruso M., Testa A., Mauceri G., Borsellino N., Chiarenza M. *et al.*: "Vinorelbine and cisplatin for the treatment of recurrent and/or metastatic carcinoma of the uterine cervix". *Oncology*, 2002, *63,* 31.
[20] Wagenaar H.C., Pecorelli S., Mangioni C., van der Burg M.E., Rotmensz N., Anastasopoulou A. *et al.*: "Phase II study of mitomycin-C and cisplatin in disseminated, squamous cell carcinoma of the uterine cervix. A European Organization for Research and Treatment of Cancer (EORTC) Gynecological Cancer Group study". *Eur. J. Cancer,* 2001, *37,* 1624.
[21] Eralp Y., Saip P., Sakar B., Kucucuk S., Aydiner A., Dincer M. *et al.*: "Prognostic factors and survival in patients with metastatic or recurrent carcinoma of the uterine cervix". *Int. J. Gynecol. Cancer,* 2003, *13,* 497.
[22] del Carmen M.G., McIntyre J.F., Goodman A.: "The role of intraoperative radiation therapy (IORT) in the treatment of locally advanced gynecologic malignancies". *Oncologist*, 2000, *5,* 18.
[23] Gemignani M.L., Alektiar K. M., Leitao M., Mychalczak B., Chi D., Venkatraman E. *et al.*: "Radical surgical resection and high-dose intraoperative radiation therapy (HDR-IORT) in patients with recurrent gynecologic cancers". Int. J. Radiat. Oncol. Biol. Phys., 2001, *50*, 687.
[24] Hockel M.: "Laterally extended endopelvic resection: Surgical treatment of infrailiac pelvic wall recurrences of gynecology malignancies". *Am. J. Obstet. Gynecol.,* 1999, *180,* 306.
[25] Hockel M.: "Laterally extended endopelvic resection. Novel surgical treatment of locally recurrent cervical carcinoma involving the pelvic sidewall". *Gynecol. Oncol.*, 2003, *9,* 369.
[26] Lopez-Graniel C., Dolores R., Cetina L, Gonzalez A., Cantu D., Chanona J. *et al.*: "Pre-exenterative chemotherapy, a novel therapeutic approach for patients with persistent or recurrent cervical cancer". *BMC Cancer,* 2005, *5,* 118.

Address reprint requests to:
W.A.A. TJALMA, M.D.
Department of Gynecology
and Gynecological Oncology
University Hospital Antwerp
Wilrijkstraat 10
2650 Edegem - Antwerpen
(Belgium)