Current state-of-the-art of concomitant chemoradiation in cervical carcinomas

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Summary

Despite screening programs, cervical carcinoma remains a major health problem throughout the world. Until recently pelvic radiation has been the standard therapy for advanced disease with overall five-year survival rates of 50%. Recently, five randomized trials demonstrated a significant survival advantage for the concomitant administration of radiotherapy and cisplatin-based chemotherapy. Although the trials vary somewhat in terms of stage of disease, dose of radiation, and schedule of radiation and cisplatin, they all demonstrated a significant survival benefit for the combined approach. Congruent to these findings are results from a meta-analysis based on the data from 19 trials with 4,580 randomized patients. The absolute increase in progression-free and overall survival was 16% and 12%, respectively. Contrary to these findings is the result of the National Cancer Institute of Canada (NCCI) trial. Despite that result cisplatin-based concomitant chemoradiotherapy has become the standard treatment of locally advanced cervical cancer.

Key words: Cervical cancer; Concomitant chemoradiotherapy; Cisplatin.

Introduction

Cervical cancer is one of the most common cancers among women worldwide [1]. As many as 750,000 cases are estimated to occur annually, which would make it the most frequent female cancer in the world [2]. Despite the existence of screening programs with the aim of detecting cervical carcinoma in its early stages, many of them are discovered in later, locally advanced stages. Due to the fact that cervical cancer affects younger women more frequently than other malignancies, on average 26 years of life can be saved per patient with successful treatment of that disease [3]. Until recently pelvic radiation has been the standard therapy for advanced disease with overall five-year survival rates of 50% [4]. The main cause of death among the patients with advanced cervical carcinoma is uncontrolled disease within the pelvis. In order to improve local and distant control of the tumor, concomitant application of chemotherapy and radiotherapy has been tested.

Chemotherapy and radiotherapy can be delivered in three primary schedules: sequentially, alternatively, and concomitantly. In contrast to the sequential and altering approach, in the concomitant schedule radiation therapy and chemotherapy are initiated together. This approach has the advantage of not delaying a potentially curative therapy, i.e. radiotherapy. In addition, this strategy minimizes the risk of developing cross-resistant tumor cells because there is no interval between the two techniques. The concomitant therapy schedule, however, exerts the most severe toxicities of all forms of combined treatment modalities [5].

In February 1999, the National Cancer Institute (NCI) announced that five randomized phase III trials showed an overall survival advantage for cisplatin-based chemotherapy given concurrently with radiotherapy [6-10]. Although the trials varied somewhat in terms of the stage of disease, dose of radiation, and schedule of radiation and cisplatin, they all demonstrated a significant survival benefit for the combined approach. The risk of death from cervical cancer was decreased by 30% to 50% by concurrent chemoirradiation. Based on these results the NCI proposed cisplatin-based concurrent chemoradiotherapy as the standard treatment of women with advanced cervical cancer [11].

Background and rationale of chemoradiotherapy

The combination of chemotherapy and radiotherapy has been used in cancer management for over 35 years. The objective of chemoradiotherapy is to improve survival by increasing local-regional control by the synergistic interaction of the two cytotoxic modalities on the one hand and by reducing distant metastases by means of the action of the cytotoxic drugs on sites that are not irradiated on the other hand.

The exact mechanisms of the interactions between radiotherapy and chemotherapy are not yet completely known. The prevention of the appearance of resistant clones of tumor cells may be one of the mechanisms. Tumor cells resistant to one modality may be sensitive to others. The Goldie-Coldman hypothesis assumes that the number of tumor cells resistant to cytotoxic drugs and/or radiotherapy increase according to the number of clonogenic cells and fre-

quency of mutations [12]. Based on that hypothesis, early eradication of resistant cells with a second modality may prevent the development of resistant clones of tumor cells. When chemotherapy is used in conjunction with radiotherapy it may increase response of tumor cells to irradiation through various mechanisms. These include the synchronisation of the cell cycle by chemotherapy to move most of the tumor cells into a radiation-sensitive phase such as G2/M-phase of the cell cycle (e.g., paclitaxel, hydroxyurea), a direct toxicity of hypoxic cells (e.g., mitomycin-C), oxygenation of hypoxic cells (e.g., cisplatin), and inhibition of repair of sublethal or potentially lethal radiation induced damage (cisplatin, anthracyclines) [13, 14]. Another, potentially important mechanism of chemoradiotherapy interaction is the inhibition of repopulation of tumor cells. An accelerated repopulation of tumor cells may occur during fractionated irradiation and may result in failure of treatment [15]. Concomitant chemotherapy may slow the rate of repopulation and therefore increase the effectiveness of the treatment.

Cervical carcinoma is a local disease and the majority of patients dying due to cervical cancer are dying because of the uncontrolled local disease. It is logical to conclude that increased local control will result in improved survival of patients with locally advanced cervical cancer. Until recently the standard treatment of patients with locally advanced cervical carcinoma was definitive radiotherapy. The high incidence of both local and distant recurrences in patients with Stage III disease treated by standard radiotherapy protocols, i.e. doses of 80-85 Gy produced combining intracavitary brachy- and external radiotherapy to point A, suggests the need for additional therapeutic modalities that will decrease the local failure rate as well as the incidence of distant metastases. Higher doses of radiotherapy may reduce the local failure rates, but this therapeutic approach is associated with a considerable increase in early and late damage of normal tissue structures that are involved in the irradiated fields [16, 17]. The implementation of a low-dose rate (LDR)- instead of high dose rate (HDR)-brachyradiotherapy provides the possibility to increase the local radiation dose or to decrease the incidence and degree of early and late damage [18].

Chemotherapy is not the first-line therapy of locally advanced carcinoma of the cervix uteri. Despite the findings of an objective response to chemotherapeutic agents, a survival advantage has not been seen [19]. The rational step in the possible improvement concerning the treatment of locally advanced cervical carcinoma has been the implementation of concurrent chemoirradiation. The most often used drug in the treatment of cervical cancer is cisplatin [20]. Except for its direct activity against tumor cells, cisplatin has been shown to enhance the cytotoxic effects of radiation therapy in various tumors, both in vitro and in vivo [21]. Although the precise mechanism by which cisplatin increases radiation-induced cytotoxicity has not yet been defined, the inhibition of repair mechanisms of sublethal radiation-induced damage and sensitisation of hypoxic cells have been postulated as possibilities [22].

Randomized prospective clinical studies

In 1999, the results of five multicentric, randomized, controlled trials were published demonstrating a statistically significant survival advantage for the concomitant chemoradiotherapy of patients with locally advanced cervical cancer [6-10].

In three out of these five trials patients with very advanced disease were enrolled [8-10]. Despite the differences with regards to the inclusion criteria, chemotherapy schedules, and radiotherapy protocols, all studies demonstrated an absolute improvement in survival between 9%-18% for concurrent chemoradiotherapy in comparison to radiotherapy alone (Table 1). Based on these results and the subsequent NCI announcement the treatment of advanced cervical cancer changed throughout the world, and, today, the golden standard of treatment is concomitant chemoradiotherapy, usually with the weekly application of cisplatin during external radiotherapy according to Rose *et al.* [10].

Rose *et al.* [10] randomized 526 patients with FIGO Stages IIB - IVA to receive either weekly cisplatin alone or two cycles of a cisplatin- and fluorouracil-containing regimen or hydroxyurea alone, each in combination with standard radiotherapy. After a median follow-up of 35 months both groups of patients who had received a cisplatin-containing chemotherapy had a statistically significantly better progression-free and overall survival than the group that had received hydroxyurea alone. The relative risk of disease progression or death was 0.57 and 0.55, respectively, for patients who had received cisplatin-based chemotherapy concomitantly with radiotherapy in comparison to the patients who had received hydroxyurea alone in combination with radiotherapy. Significantly lower rates of distant and loco-regional relapses were detected in the concomitant chemoradiotherapy arms suggesting a synergistic local as well as an independent systemic action of the cytotoxic drugs.

Table 1. — *Major characteristics of randomized trials of concomitant chemoradiotherapy.*

Author	FIGO stages	CT regimen	Overall survival		Median Follow-up
			Combined treatment	Radiotherapy only	
Whitney	IIB-IVA	CF x 2	55%	43%	8.7 years
Rose	IIB-IVA	C x 6	66%	50%	3 yrs
	CHF x 2	67%			
Morris	IIB-IVA or IB2-IIA (> 5 cm or PLN+)	CF x 3	73%	58%	3.6 yrs
Peters	IA2-IIA + PLN+ and/or positive margins and/or microscopic parametrial involvement	CF x 4	81%	71%	3.5 yrs
Keys	IB2 (> 4 cm)	C x 6	83%	74%	3 yrs
Wong	IIB-III	E x 6 (1+5)	≈79%	≈68%	6.7 yrs
Pearcey	IB-IVA	C x 5	62%	58%	5 yrs

CT: chemotherapy; C: cisplatin; F: fluorouracil; H: hydroxyurea; PLN: pelvic lymph nodes; E: epirubicin.

In the study by Morris *et al.* [9] 403 patients with cervical cancer Stages IB bulky up to IVA were randomized to receive either radiotherapy alone (pelvic plus para-aortic field) or concomitant chemotherapy with cisplatin and fluorouracil with pelvic radiotherapy. Patients randomized to the concomitant chemoradiotherapy arm of the study received two cycles of chemotherapy concurrently with external radiotherapy and a third cycle concurrently with the second low-dose rate brachyradiotherapy application. After a median follow-up of 43 months the chemoradiotherapy group had a significantly better overall and disease-free survival. The estimated cumulative 5-year survival rates were 73% for the concomitant chemoradiotherapy and 58% for radiotherapy alone. Another important finding of the study was that patients who had received radiotherapy alone showed significantly higher rates of both distant metastases and local recurrences.

The third study that enrolled patients with far advanced cervical cancer was the study by Whitney *et al.* [8]; 368 patients were randomized to receive either cisplatin and fluorouracil or hydroxyurea concomitantly with external radiotherapy. After a very long follow-up period of 8.7 years the overall and progression-free survival were significantly better in the cisplatin- containing concomitant chemoradiotherapy arm of the study. The relative risk of progression or death of the cisplatin/fluorouracil group was 0.70 compared to the hydroxyurea group. In contrast to the preceding two studies in this study no statistically significant difference regarding the incidence of distant and loco-regional relapses was found between the two treated arms although the patients receiving the cisplatin-containing chemotherapy concomitantly with radiotherapy showed a trend towards a lower incidence of distant and loco-regional relapses.

Two studies included patients with early-stage, high-risk cervical carcinoma [6, 7].

In the study by Peters *et al.* [7] 268 patients with clinical Stages IA2, IB and IIA showing high-risk pathologic factors after radical hysterectomy and pelvic lymphadenectomy, i.e. positive pelvic lymph nodes and/or positive margins and/or microscopic parametrial involvement, were enrolled; the patients were randomized to receive standard radiotherapy treatment or a concomitant chemoradiotherapy with four cycles of cisplatin/fluorouracil. Two chemotherapy cycles were applied concomitantly with external radiotherapy and two after the completion of the concomitant chemoradiotherapy as an adjuvant or consolidation chemotherapy. Again, overall and progression-free survival was significantly better in patients receiving concomitant chemoradiotherapy. After a median follow-up of 42 months the estimated 4-year survival rate was 81% for the chemotherapy-containing arm and 71% for the standard radiotherapy arm. In this study, consistently with the others mentioned before, a trend towards a lower incidence of distant and loco-regional relapses was observed in the group of patients receiving chemotherapy. A very interesting finding of this study was the increased survival of patients receiving three or four cycles of chemotherapy versus patients receiving only one or two cycles suggesting that the chemotherapy was having an effect independent of radiotherapy.

The second study enrolling patients with early stage disease (IB2) was the study by Keys *et al.* [6]; 374 patients were randomized to receive radiotherapy alone or radiotherapy plus weekly cisplatin. After the completion of the assigned treatment, all patients were subjected to adjuvant hysterectomy. After a median follow-up of 36 months the overall and progression-free survival times were significantly better in the concomitant chemoradiotherapy arm of the study. The relative risk of death in the combined-therapy group was 0.54 in comparison to the group receiving radiotherapy only. In this study, patients receiving the combined treatment showed a significantly lower incidence of loco-regional relapses in comparison to the patients receiving radiotherapy only. The authors did not state the results regarding the incidence of distant metastases.

As expected, the incidence of side-effects was higher in the group of patients treated with combined treatment. The severity of the side-effects was higher in the concomitant chemoradiotherapy group as well. Nevertheless, these side-effects were usually self-limited or resolved with medical management. The most common side-effects were leukopenia, thrombocytopenia, anaemia, and bowel and bladder complications. The incidences or severity of late complications were not different between the combined treatment group and the radiotherapy only group.

Congruent to the above described findings are the results published by Wong *et al.* [23]. In their study patients were randomized to receive either standard pelvic radiotherapy alone or the identical radiotherapy plus epirubicin at a dose of 60 mg/m^2 on the day of commencement of radiotherapy followed by adjuvant chemotherapy with epirubicin 90 mg/m^2 administered at 4-week intervals for five additional cycles. After a median follow-up of 77 months patients who received irradiation plus epirubicin demonstrated a significantly longer disease-free and overall survival than those treated with radiotherapy alone (Table 1). Moreover, the addition of epirubicin significantly decreased the incidence of distant metastases.

In contrast to the results of the studies described before are the results of the study published by Pearcey *et al.* [24]. In this study 259 patients with FIGO Stages IB to IVA were randomized to receive either radiotherapy plus weekly cisplatin (40 mg/m^2) or the same radiotherapy without chemotherapy. After a median follow-up of 82 months no significant differences with respect to progression-free and overall survival at three and five years were found (Table 1). The authors tried to find possible explanations for the differences between the results of their trial and the preceding studies.

The first explanation was that concomitant chemoradiotherapy adds no benefit to properly executed radiotherapy. The median length of radiotherapy treatment in their study was 51 days in comparison to 62 and 64 days, respectively, in the studies by Rose and Whitney. It is well known that prolongation of radiotherapy may result in inferior local control rates [25]. The second explanation was related to the level of hemoglobin during the treatment. Pearcey et al. found a significant decrease in the hemoglobin level in the concomitant chemoradiotherapy arm in comparison to the

radiotherapy only arm. Grogan *et al.* had already demonstrated the impact of maintaining hemoglobin values during radiotherapy treatment [26]; in their study an advantage of 29% in the 5-year survival rates was observed for patients with an average weekly nadir hemoglobin above 120 g/l versus those with values of less than 110 g/l. The difference in hemoglobin level observed in the study by Pearcey *et al.* could have accounted for as much as an 8% reduction in survival in the concomitant chemoradiotherapy arm of the study. The third explanation for the different results might be the staging system used in the different trials. In contrast to the studies by Rose, Whitney and Morris where most of the patients were surgically staged (to rule out para-aortic lymph node metastases) in the trial by Pearcey *et al.* the patients were not surgically staged. It could be speculated that the survival advantage observed in the other studies was lost in the trial by Pearcey et al. due to a larger percentage of patients with subclinical para-aortic lymph node involvement. The last explanation is that the study of Pearcey et al. was designed to detect a 15% improvement in the 5-year survival rate with 80% power. Thus, it is possible that a smaller, but still clinically significant difference in survival was not detected. In summary, the authors concluded that the balance of evidence favors the use of combined-modality treatment for patients with locally advanced cervical cancer.

Meta analysis results

The results of a meta-analysis published by Green et al. provide further evidence favoring the use of concomitant chemoradiotherapy [27]. The authors analysed the results from 19 prospective, randomized trials including a total of 4,580 patients. This meta-analysis showed that concomitant chemoradiotherapy improves overall survival with a hazard ratio of 0.71. The absolute benefits in progression-free and overall survival were 16% and 12%, respectively. The rate of distant metastases was significantly decreased in the patients receiving chemoradiotherapy with an odds ratio of 0.57 ($p < 0.0001$). Similarly, the rate of local recurrences was significantly reduced by chemoradiotherapy with an odds ratio of 0.61 ($p < 0.0001$). Another important result of this meta-analysis was the finding that the effect of concomitant chemoradiotherapy on survival was irrespective of the type of chemotherapy, i.e. cisplatin-based or non-cisplatin-based. As their results derived from trials of different populations, with different treatment regimens and different supportive care facilities the authors conclude that these results are potentially generalizable.

Potential future directions - issues to be resolved

A number of questions regarding concomitant chemoradiotherapy remain unanswered:

What is the ideal chemotherapeutic drug or drug combination to be used concomitantly with radiotherapy?

What is the best time to apply chemotherapy during radiotherapy, i.e. during external radiotherapy as in current practice or during brachyradiotherapy applications when the highest dose of radiation is given?

What is the role of consolidation (or adjuvant) chemotherapy in the treatment of advanced cervical cancer?

What is the role of hemoglobin levels during concomitant chemoradiotherapy?

Many different drugs have been investigated in this setting of concurrent chemoradiotherapy. The meta-analysis by Green *et al.* showed that, besides cisplatin, many other cytotoxic drugs do exert synergistic effects when applied concomitantly with radiotherapy [27]. The results published by Rose et al. showed that cisplatin is equal in efficacy and better in safety compared to a combination of cisplatin and 5-fluorouracil. Will any other drug combination be better than cisplatin monochemotherapy? This question should be investigated in future trials.

The concept of applying chemotherapy concurrently with brachyradiotherapy is very interesting because, when chemotherapy is applied concomitantly with brachyradiotherapy, it is combined with an up to 15-fold higher dose of irradiation compared to its application concomitantly to external radiation. Thus, it is logical to postulate that the synergistic effects of such a combination could be significantly greater than if the same chemotherapy is combined with external radiation.

Consolidation or adjuvant therapy could have a very important role in the treatment of patients with advanced cervical cancer. Peters *et al.* showed that patients receiving three or four cycles of chemotherapy had an increased survival compared to those patients receiving only one or two cycles suggesting that the chemotherapy was having an effect independent of radiotherapy [7]. Moreover, the known positive impact of adjuvant chemotherapy on recurrence-free and overall survival rates of colon or breast cancer patients is encouraging.

The hemoglobin levels during chemoradiotherapy are apparently of great importance [26]. The results of the retrospective study by Grogan *et al.* showed that patients with an average weekly nadir hemoglobin (AWNH) value of less than 110 g/l have a 29% lower 5-year survival rate than those patients with AWNH levels above 120 g/l. Prospective trials have been initiated in order to confirm this finding. Before we have answers from these studies we should try to maintain the AWNH level of patients undergoing concomitant chemoradiotherapy above 110 g/l.

Recently Vrdoljak *et al.* presented the results of their phase II study that was conducted to find some potential answers to the above-mentioned questions [28]. They tested a combination of the two most efficacious single-agent drugs for the treatment of advanced cervical cancer, i.e. cisplatin and ifosfamide, applied concomitantly to two low-dose-rate brachyradiotherapy insertions. The rationale for that approach is the synergism between ifosfamide and low-dose-rate radiotherapy, as previously shown by Tonkin *et al.* [29], and furthermore the fact that 60 Gy out of the total dose of 85 Gy given to point A are given by those brachyradiotherapy insertions. Moreover, low-dose-rate brachyra-

diotherapy, as every brachytherapy, is less damaging to late responding tissues and is directed more to the tumor than to normal surrounding tissues [18]. They also tested in their study the efficacy and toxicity of four cycles of consolidation chemotherapy with cisplatin plus ifosfamide applied after the completion of concurrent chemo (brachy) radiotherapy. Their results, a 100% clinical response rate, a 95% overall and 93% disease-free survival after a median follow-up of 19 months, indicate that this treatment of advanced cervical cancer may be advantageous in comparison with the standard one.

In conclusion, until all the above-mentioned questions have been answered, concomitant chemoradiotherapy based on weekly cisplatin applications with external radiotherapy is the treatment of choice for advanced cervical cancer.

References

[1] Parker S., Tong T., Bolden S. *et. al.*: "Cancer Statistic". 1996, *CA Cancer J. Clin.,* 1996, *46*, 5.

[2] Advances in the treatment of cervical cancer. "International Network for Cancer Treatment and Research". Belgium, 20 April, 2001 Meeting.

[3] Average years of life lost from cancer. *J. Natl. Cancer Inst.*, 1993, *201,* 2341.

[4] Coia L., Won M., Lanciano R. *et al.*: "The patterns of care outcome study for cancer of the uterine cancer: Results of the Second National Practice Survey". *Cancer,* 1990, *66,* 2451.

[5] Dorr R.T., Fritz W.L.: "Cancer Chemotherapy Handbook". New York, NY, Elsevier, 1980.

[6] Keys H.M., Bundy B.N., Stehman F.B. *et al.*: "Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma". *N. Engl. J. Med.,* 1999, *340*, 1154.

[7] Peters W.A., Liu P.Y., Barrett R.J. *et al.*: "Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix". *J. Clin. Oncol.,* 2000, *18,* 1606.

[8] Whitney C.W., Sause W., Bundy B.N. *et al.*: "Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in Stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: A Gynecologic Oncology Group and Southwest Oncology Group Study". *J. Clin. Oncol.,* 1999, *17*, 1339.

[9] Morris M., Eifel P.J., Lu J. *et al.*: "Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer". *N. Engl. J. Med.,* 1999, *340*, 1137.

[10] Rose P.G., Bundy B.N., Watkins E.B. *et al.*: "Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer". *N. Engl. J. Med.*, 1999, *340*, 1144.

[11] National Cancer Institute: NCI Clinical Announcement. Bethesda, M.D., United States Department of Health and Human Services, Public Health Service, National Institutes of Health, February 1999.

[12] Goldie J.H., Coldman A.J.: "A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate". *Cancer Treat. Rep.*, 1979, *63*, 1727.

[13] Dewit L.: "Combined treatment of radiation and cis-diamminedichloroplatinum (II): A review of experimental and clinical data". *Int. J. Radiat. Oncol. Biol. Phys.*, 1987, *13*, 403.

[14] Douple E.B.: "Platinum-radiation interactions". *NCI Monogr.,* 1988, *6,* 315.

[15] Withers H.R., Taylor J.M.G., Maciejewski B.: "The hazard of accelerated tumor clonogen repopulation during radiotherapy". *Acta Oncol.*, 1988, *27,* 131.

[16] Perez C.A., Fox S., Lockett M.A. *et al.*: "Impact of dose in outcome of irradiation alone in carcinoma of the uterine cervix: Analysis of two different methods". *Int. J. Radiat. Oncol. Biol. Phys.,* 1991, *21,* 885.

[17] Pederson D., Bentzen S.M., Overgaad J.: "Early and late radiotherapeutic morbidity in 442 consecutive patients with locally advanced carcinoma of the uterine cervix". *Int. J. Radiat. Oncol. Biol. Phys.,* 1994, *29,* 941.

[18] Teshima T., Inoue T., Ikeda H. *et al.*: "High dose rate and low dose rate intracavitary therapy for carcinoma of the uterine cervix". *Cancer,* 1993, *72,* 2409.

[19] Omura G.A.: "Current status of chemotherapy for cervix cancer". *Oncology,* 1992, *6*, 27.

[20] Thigpen T., Shingleton H., Homesley H. *et al.*: "Cis-platinum in treatment of advanced or recurrent squamous cell carcinoma of the cervix". *Cancer,* 1981, *48*, 899.

[21] Fu K.K., Lam K.N., Rayner P.A.: "The influence of time sequence of Cisplatin administration and continuous low dose rate irradiation (CLDRI) on their combined effects on a murine squamous cell carcinoma". *Int. J. Radiat. Oncol. Biol. Phys.,* 1985, *11,* 21.

[22] Douple E.B., Richmond R.C.: "A review of interaction between platinum coordination complexes and ionizing radiation: Implication for cancer therapy". In: Prestayko A.W., Crooke S.T., Carter S.K. (eds.): "Cisplatin Current Status and New Developments". New York, NY, Academic Press, 1980, 125.

[23] Wong L.C., Ngan H.Y.S., Cheung A.N.Y. *et al.*: "Chemoradiation and adjuvant chemotherapy in cervical cancer". *J. Clin. Oncol.,* 1999, *17*, 2055.

[24] Pearcey R., Brundage M., Drouin P. *et al.*: "Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix". *J. Clin. Oncol.,* 2002, *20*, 966.

[25] Fyles A.W., Pintile M., Kirkbride P. et al.: "Prognostic factors in patients with cervix cancer treated by radiation therapy: Results of a multiple regression analysis". *Radiother. Oncol.,* 1995, *35,* 107.

[26] Grogan M., Thomas G.M., Melamed I. et al.: "The importance of hemoglobin levels during radiotherapy for carcinoma of the cervix". *Cancer,* 1999, *86*, 1528.

[27] Green J.A., Kirwan J.M., Tierney J.F. *et al.*: "Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis". *Lancet,* 2001, *358*, 781.

[28] Vrdoljak E., Prskalo T., Frleta Ilic N. *et al.*: "Concomitant chemobrachyradiotherapy with ifosfamide and cisplatin followed by consolidation chemotherapy in locally advanced squamous cell carcinoma (LASCC) of the cervix uteri: results of a phase II study". *Gynecol. Oncol.,* 2003, *88*, 194 (abstr 79).

[29] Tonkin K.S., Kelland L.R., Steel G.G.: "Chemotherapy-radiation interactions in human cervix carcinoma xenografts". *Br. J. Cancer,* 1988, *58,* 738.

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