REVIEW

Concurrent Radiotherapy and Chemotherapy of Cervical Cancer

Cemil **YAMAN**[1], Michael **FRIDRICK**[2]

[1]*Department of Obstetrics & Gynecology, AKH-Linz, Krankenhausstr. 9, A-4020 Linz, Austria*
[2]*Department of Oncology, AKH-Linz, Krankenhausstr. 9, A-4020 Linz, Austria*

Received 26 December 2004; received in revised form 5 January 2005; accepted 21 January 2005

Abstract

Prospective, randomized trials conducted over the past 10 years have changed the management of patients with advanced cervical cancer. Overall and progression-free survivals were superior for patients receiving cisplatin-based combination radiochemotherapy than that of radiotherapy. Lymph node status needs to be evaluated before treatment by laparoscopy. Paraaortic radiotherapy should be performed only in patients with positive paraaortic lymph nodes. Higher rate of reversible hematologic and gastrointestinal toxicity effects in the combined-therapy group.

Keywords: cervical cancer, radiotherapy, chemotherapy

Özet

Serviks Kanserinde Eşzamanlı Radyoterapi ve Kemoterapi

Son on yıl içinde yapılan prospektif randomize çalışmalar ile ileri evre servikal kanserin tedavisi konusunda değişiklikler olmuştur. Toplam ve progresyon olmayan hasta survisi, sisplatin temelli kombinasyon radyokemoterapisi alan olgularda sadece radyoterapi alan olgulara göre daha iyi olarak bulunmuştur. Tedavi öncesinde laparoskopi ile lenf nodu durumunun değerlendirilmesi gerekmektedir. Paraaortik radyoterapi sadece paraaortik lenf nodu pozitifliği olan hastalar için planlanmalıdır. Kombine terapi grubunda hemotolojik ve gastrointestinal toksisitenin daha yüksek oranda geri dönüşümlü olduğu tespit edilmiştir.

Anahtar sözcükler: serviks kanseri, radyoterapi, kemoterapi

Introduction

Although screening for cervical cancer is readily available, most women who are found to have cervical cancer were not screened regularly. As a result, many patients with cervical cancer present advanced disease anywhere from stage Figo IIB through Figo IV.

Radiation therapy plays a major role in the management of patients with cervical cancer. It is a primary treatment for those with advanced disease and reduces local recurrences after surgery.

The ability of radiotherapy to cure locally advanced cervical cancer is limited by the size of the tumor, because the doses required to treat large tumors exceed the limit of toxicity in normal tissue. Radiotherapy is used for treatment of local diseases while chemotherapy is used for treatment of systemic disease. Moreover, chemotherapy might increase the sensitivity of the tumor to radiation. Therefore chemotherapy and radiotherapy could have a synergistic effect.

This review article gives a summary about the published randomized clinical studies regarding the therapeutic value of concurrent radio and chemotherapy in women with locally advanced cervical cancer.

Review

Morris et al. (1) compared the effect of radiotherapy to a pelvic and para-aortic field with that of pelvic radiation and concurrent chemotherapy with fluorouracil and cisplatin in women with advanced cervical cancer. 403 women with advanced cervical cancer confined to the pelvis (stages IIB through IVA or stage IB or IIa with a tumor diameter of at least 5 cm or involvement of pelvic lymph nodes) were randomly assigned to receive either 45 Gy of radiation to the pelvis and para-aortic lymph nodes or 45 Gy of radiation to the pelvis alone plus two cycles of fluorouracil and cisplatin (days 1 through 5 and days 22 through 26 of radiation). Patients were then

Corresponding Author: Univ.-Doz. Dr. Cemil Yaman
General Hospital of Linz, Krankenhausstr
9 A-4020 Linz, Austria
Phone : +43 732 7806 73389
Fax : +43 732 7806 2226
E-mail : cemil.yaman@akh.linz.at

to receive one or two applications of low-dose-rate intracavitary radiation, with a third cycle of chemotherapy planned for the second intracavitary procedure in the combined-therapy group. Of the 403 eligible patients, 193 in each group could be evaluated. The median duration of follow-up was 43 months. Estimated cumulative rates of survival at five years were 73% among patients treated with radiotherapy and chemotherapy and 58% among patients treated with radiotherapy alone (P=0.004). Cumulative rates of disease-free survival at five years were 67% among patients in the combined-therapy group and 40% among patients in the radiotherapy group (P<0.001). The rates of both distant metastases (P<0.001) and locoregional recurrences (P<0.001) were significantly higher among patients treated with radiotherapy alone. The seriousness of side effects was similar in the two groups, with a higher rate of reversible hematologic effects in the combined-therapy group. The addition of chemotherapy with fluorouracil and cisplatin to treatment with external-beam and intracavitary radiation significantly improved survival among women with locally advanced cervical cancer.

Rose et al. (2) performed a randomized trial of radiotherapy in combination with three concurrent chemotherapy regimens — cisplatin alone; cisplatin, fluorouracil, and hydroxyurea; and hydroxyurea alone — in patients with locally advanced cervical cancer. Women with primary untreated invasive squamous-cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix of stage IIB, III, or IVA, without involvement of the para-aortic lymph nodes, were enrolled. All patients received external-beam radiotherapy according to a strict protocol. Patients were randomly assigned to receive one of three chemotherapy regimens: 40 mg of cisplatin per square meter of body-surface area per week for six weeks (group 1); 50 mg of cisplatin per square meter on days 1 and 29, followed by 4 g of fluorouracil per square meter given as a 96-hour infusion on days 1 and 29, and 2 g of oral hydroxyurea per square meter twice weekly for six weeks (group 2); or 3 g of oral hydroxyurea per square meter twice weekly for six weeks (group 3).

The analysis included 526 women. The median duration of follow-up was 35 months. Both groups that received cisplatin had a higher rate of progression-free survival than the group that received hydroxyurea alone (P<0.001 for both comparisons). The relative risks of progression of disease or death were 0.57 (95% confidence interval, 0.42 to 0.78) in group 1 and 0.55 (95% confidence interval, 0.40 to 0.75) in group 2, as compared with group 3. The overall survival rate was significantly higher in groups 1 and 2 than in group 3, with relative risks of death of 0.61 (95% confidence interval, 0.44 to 0.85) and 0.58 (95% confidence interval, 0.41 to 0.81), respectively. Regimens of radiotherapy and chemotherapy that contain cisplatin improve the rates of survival and progression-free survival among women with locally advanced cervical cancer.

Peters al. (3) determined whether the addition of cisplatin-based chemotherapy (CT) to pelvic radiation therapy (RT) will improve the survival of early-stage, high-risk patients with cervical carcinoma. Patients with clinical stage IA(2), IB, and IIA carcinoma of the cervix, initially treated with radical hysterectomy and pelvic lymphadenectomy, and who had positive pelvic lymph nodes and/or positive margins and/or microscopic involvement of the parametrium were eligible for this study. Patients were randomized to receive RT or RT + CT. Patients in each group received 49.3 GY RT in 29 fractions to a standard pelvic field. Chemotherapy consisted of bolus cisplatin 70 mg/m^2 and a 96-hour infusion of fluorouracil 1,000 mg/m^2/d every 3 weeks for four cycles, with the first and second cycles given concurrent to RT. Two hundred forty-three patients were assessable (127 RT + CT patients and 116 RT patients). Progression-free and overall survivals were significantly improved in the patients receiving CT. The hazard ratios for progression-free survival and overall survival in the RT only arm versus the RT + CT arm were 2.01 (P =0.003) and 1.96 (P =0.007), respectively. The projected progression-free survivals at 4 years is 63% with RT and 80% with RT + CT. The projected overall survival rate at 4 years is 71% with RT and 81% with RT + CT. Grades 3 and 4 hematologic and gastrointestinal toxicity were more frequent in the RT + CT group.

The addition of concurrent cisplatin-based CT to RT significantly improved progression-free and overall survival for high-risk, early-stage patients who undergo radical hysterectomy and pelvic lymphadenectomy for carcinoma of the cervix.

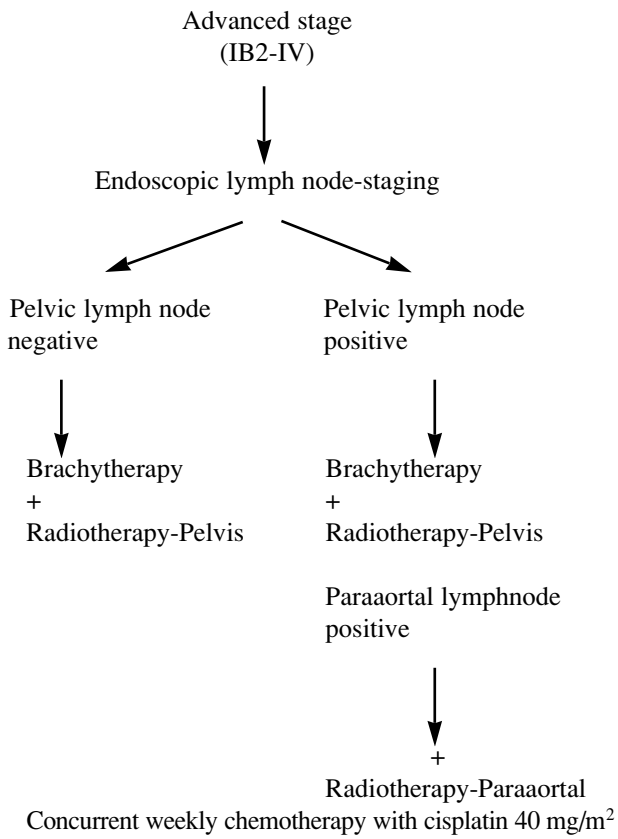
Keys et al. (4) determined whether weekly infusions of cisplatin during radiotherapy improve progression-free and overall survival among patients with bulky stage IB cervical cancer. Women with bulky stage IB cervical cancers (tumor, >4 cm or =4 cm in diameter) were randomly assigned to receive radiotherapy alone or in combination with cisplatin (40 mg per square meter of body-surface area once a week for up to six doses; maximal weekly dose, 70 mg), followed in all patients by adjuvant hysterectomy. Women with evidence of lymphadenopathy on computed tomographic scanning or lymphangiography were ineligible unless histologic analysis showed that there was no lymph-node involvement. The cumulative dose of external pelvic and intracavitary radiation was 75 Gy to point A (cervical parametrium) and 55 Gy to point B (pelvic wall). Cisplatin was given during external radiotherapy, and adjuvant hysterectomy was performed three to six weeks later.

The relative risks of progression of disease and death among the 183 women assigned to receive radiotherapy and chemotherapy with cisplatin, as compared with the 186 women assigned to receive radiotherapy alone, were 0.51 (95% confidence interval, 0.34 to 0.75) and 0.54 (95% confidence interval, 0.34 to 0.86), respectively. The rates of both progression-free survival (P<0.001) and overall survival (P=0.008) were significantly higher in the combined-therapy group at four years. In the combined-therapy group there were higher frequencies of transient grade 3 (moderate) and grade 4 (severe) adverse hematologic effects (21%, vs. 2% in the radiotherapy group) and adverse gastrointestinal effects (14% vs. 5%).

Conclusions: Adding weekly infusions of cisplatin to pelvic radiotherapy followed by hysterectomy significantly reduced the risk of disease recurrence and death in women with bulky stage IB cervical cancers.

Eifel et al. (5) reported mature results of a randomized trial that compared extended-field radiotherapy (EFRT) versus pelvic radiotherapy with concomitant fluorouracil and cisplatin (CTRT) in women with locoregionally advanced carcinomas of the uterine cervix. 403 women with cervical cancer were randomly assigned to receive either EFRT or CTRT. Patients were eligible if they had stage IIB to IVA disease, stage IB to IIA disease with a tumor diameter >5 cm or = 5 cm, or positive pelvic lymph nodes. Patients were stratified by stage and by method of lymph node evaluation. The median duration of follow-up for 228 surviving patients was 6.6 years. The overall survival rate for patients treated with CTRT was significantly greater than that for patients treated with EFRT (67% vs. 41% at 8 years; P <0.0001). There was an overall reduction in the risk of disease recurrence of 51% (95% CI, 36% to 66%) for patients who received CTRT. Patients with stage IB to IIB disease who received CTRT had better overall and disease-free survival than those treated with EFRT (P<0.0001); 116 patients with stage III to IVA disease had better disease-free survival (P=0.05) and a trend toward better overall survival (P=0.07) if they were randomly assigned to CTRT. The rate of serious late complications of treatment was similar for the two treatment arms. Mature analysis confirmed that the addition of fluorouracil and cisplatin to radiotherapy significantly improved the survival rate of women with locally advanced cervical cancer without increasing the rate of late treatment-related side effects.

Table 1. Treatment of cervical cancer



Concurrent weekly chemotherapy with cisplatin 40 mg/m^2

Conclusion

The results of published randomized trials have demonstrated a significant improvement in pelvic disease survival when concurrent cisplatin-based chemotherapy was added to radiation therapy for both advanced cervical cancer and early cancer with positive lymph nodes. Lypmh node staging should be performed to determine the extent of radiation (Table 1).

References

1. Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE, Rotman M, Gershenson DM, Mutch DG. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med. 1999;340(15):1137-43.
2. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, Clarke-Pearson DL, Insalaco S. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med. 1999;340(15):1144-53. Erratum in: N Engl J Med. 1999;341(9):708.
3. Peters WA 3rd, Liu PY, Barrett RJ 2nd, Stock RJ, Monk BJ, Berek JS, Souhami L, Grigsby P, Gordon W Jr, Alberts DS. 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(8):1606-13.
4. Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Suggs CL 3rd, Walker JL, Gersell D. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med. 1999;340(15):1154-61. Erratum in: N Engl J Med. 1999;341(9):708.
5. Eifel PJ, Winter K, Morris M, Levenback C, Grigsby PW, Cooper J, Rotman M, Gershenson D, Mutch DG. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. J Clin Oncol. 2004;22(5):872-80.