Combined external and intracavitary irradiation in treatment of advanced cervical carcinomas: Predictive factors for local tumor control and early recurrences

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Abstract. In a series of 131 primary cervical carcinomas in FIGO stages I-IV suitable for combined external pelvic and intraluminal cervical-vaginal brachytherapy predictive and prognostic factors were analyzed with regard to locoregional tumor control, recurrences and survival data. Patients with prior surgery or patients treated with external beam therapy alone were excluded from this series. Concomitant chemotherapy was given to 47 patients (36%). The external beam therapy was given with a four-field technique (50-60 Gy) and brachytherapy with high dose-rate (Ir-192) using a ring applicator set. The dose (18-30 Gy) was specified according to the rules in ICRU 38 (a minimum dose to the surface of the target volume). Three or five fractions were given once a week in parallel with external beam irradiation. A CT-based 3-D dose-planning system (TMS) was used for the external beam therapy and for the brachytherapy planning (PLATO). The mean age of the patients was 65 years. One hundred and seven tumors were squamous cell carcinomas (82%) and 24 adenocarcinomas or adenosquamous carcinomas. One hundred and eight tumors were in FIGO stages I-II and 23 tumors in stages III-IV. The mean tumor diameter was 44 mm. Most tumors (92%) were moderately well or poorly differentiated. The primary cure rate of the complete series was 92% and 98% after chemoradiotherapy. Squamous cell carcinomas had complete remission in 96% and adenocarcinomas in 81% (Pearson Chi-square; P=0.00002). Tumor size was also highly significantly associated with local tumor control. The brachytherapy dose, the combined external and brachytherapy dose and the number of days of interruption (delay) of external irradiation were all significant predictive factors of local tumor control. In the complete series 39 recurrences (30%) were recorded. A lower FIGO stage, chemoradiotherapy, squamous cell histology, diploid DNA-profile, a higher brachytherapy dose, more brachytherapy fractions and a higher total combined irradiation dose were favorable factors with regard to the risk of tumor recurrences. The overall survival rate was 50% and the cancer-specific survival rate 65%. Tumor size was the strongest individual prognostic factor in multivariate analysis. Chemoradiotherapy therapy versus radiotherapy alone and squamous cell carcinomas versus adenocarcinomas were associated with improved survival rates. Early radiation reactions were recorded in 58% (mostly grade 1) and serious late radiation reactions (grade 3-4) in 11%.

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Introduction

The incidence of cervical cancer has declined in Sweden (1) and in most of Europe due to well organized screening programs for vaginal cytology. However, on a global scale it is still the second most prevalent cancer in women, especially in developing countries (2). In the developed world most patients present with early disease either confined to the cervix or with limited extension beyond it (FIGO stages IB1-IIA). Radical hysterectomy with node dissection or radical radiotherapy are two options for these cases both giving 5-year survival rates of ~80-90% (3). For locally advanced disease (FIGO stages IIB, III and IVA) as well as for bulky stage IB (>4 cm) radical radiotherapy, comprising external beam and intracavitary treatment is the treatment of choice (4). Pelvic radiotherapy offers a good chance of cure, but the maximum radiation dose is limited by normal tissue tolerance. The risk organs are the small bowel, rectum and the bladder. The 5-year survival rate varies from 60% for patients with stage IIB disease to 20% for patients with stage IVA disease (3).

In 1999, a National Cancer Institute Alert, based on the results of 5 randomized trials recommended concomitant chemoradiation instead of radiotherapy alone in women with cervical cancer. A large benefit was shown on survival, progression-free survival and local and distant control rates (5). Concomitant chemoradiation has become standard of care for locally advanced disease. Neoadjuvant chemotherapy is another concept addressed in many studies, but its benefit in locally advanced cervical cancer warrants further exploration (6).

Brachytherapy (BT) plays a major role in the therapeutic management of patients with cervical cancer from stages I-IV.

The rapid dose fall-off allows a high central dose to the tumor, while sparing the risk organs (bladder, rectum, sigmoid and small bowel) (7). Tumor volume is a very important predictive factor in terms of local control and therefore a complete coverage of the gross tumor volume (GTV) and the related clinical target volume (CTV) is crucial and a prerequisite for the treatment outcome. The awareness of the importance of treatment planning and target volume assessment has increased substantially during the last decade (8-12). The most appropriate imaging technique is probably magnetic resonance imaging (MRI) to define tumor size, configuration and infiltration of the surrounding tissues (13-22). However, CT-scan is still used as the routine method for 3-D dose planning of cervical cancer at most centers (23-26).

In the present study, a consecutive series of 131 cervical cancer (FIGO stages I-IV) patients treated with external beam therapy and brachytherapy were evaluated retrospectively to assess treatment efficacy, side effects and important treatment related predictive factors for local tumor control and the risk of tumor recurrence. Clinical and pathological predictive and prognostic factors were also included in the analyses. This series represent cervical cancers treated with a standard technique for both external beam therapy, brachytherapy and the concomitant chemotherapy. The results will form a base of clinical outcome which are important to know before forthcoming changes are implemented in both external therapy (e.g. IMRT) and brachytherapy (3-D image based 3-D treatment planning) (26-29).

Patients and methods

During the period January 1993 to August 2006 a consecutive series of 131 cervical carcinomas in FIGO stages I-IV were treated with a combination of external beam pelvic irradiation and brachytherapy ± concomitant chemotherapy at the Department of Gynecological Oncology, Örebro University Hospital. Patients treated with primary Wertheim-Meigs surgery in FIGO stages I-II tumors as well as patients with advanced tumors in FIGO stages III-IV, not suitable for brachytherapy, were excluded from this series. Thirty-one tumors were in stage I (24%), 77 tumors in stage II (59%), 18 in stage III (14%), and 5 in stage IV (4%). In 107 cases (82%) the histology was pure squamous cell carcinomas, in 21 cases (16%) pure adenocarcinomas, and in 3 cases (2%) a mixture of both (adenosquamous carcinomas). Only 9 tumors (7%) were well differentiated, 60 tumors each (46%) moderately well and poorly differentiated, in two cases the tumors were not graded. Concomitant chemotherapy (weekly cisplatin) was given to 47 patients (36%) during the latter half of the time period (2000-2006).

All patients underwent examination under anesthesia, cystoscopy, bimanual palpation, inspection, transvaginal ultrasound, biopsy of the tumor and curettage of the cervical canal. Chest X-ray or CT, abdominal CT, and pelvic CT or MRI was part of the standard check-up of new patients. Biopsy specimens were examined with routine histopathology (type and grade), malignancy grading score (MGS), DNA analysis, and HPV-typing. Tumor tissue and serum samples were stored in a biobank at -70˚C for future genomic and proteomic studies.

Table I. Characteristics of the tumors in the complete series (n=131).

	No. of tumors	Percent
Tumor stage (FIGO)		
IB	31	23.7
IIA	32	24.4
IIB	45	34.4
IIIA	4	3.1
IIIB	14	10.7
IVA	2	1.5
IVB	3	2.3
Tumor histology		
Squamous cell carcinomas	107	81.7
Adenocarcinomas	21	16.0
Adenosquamous carcinomas	3	2.3
Tumor grade		
Well differentiated	9	6.9
Moderately well differentiated	60	45.8
Poorly differentiated	60	45.8
Not graded	2	1.5
DNA ploidy		
Diploid	46	35.1
Aneuploid	67	51.1
Tetraploid	8	6.1
Not available	10	7.6
HPV status		
Positive (16,33,35,45,56)	26	19.8
Negative	11	8.4
Not available	94	71.8

In this series, all patients received radiotherapy in a combination of external pelvic irradiation and in parallel with brachytherapy. The external beam therapy was given with a four-field box technique with the upper border at L4-L5 level, the lateral borders 1-1.5-cm lateral of the linea teminales, and the lower border 1 cm below foramina obturatoria. The dose per fraction was 2.0 Gy, given 5 days a week, and the total dose was 50 Gy (stages IB, IIA and early IIB) or 60 Gy (late IIB and III-IV). The radiation quality of the photon beams was 18 MV. The mean overall treatment time was 40 days (95% CI: 39.1-41.4 days).

The brachytherapy was given by a high-dose rate (HDR) technique (Micro-Selectron HDR; Nucletron Int. B.V., Veenendaal, The Netherlands) using an Ir-192 source. The ring applicator set (Nucletron Int. B.V.) was used with 26 mm (n=31) or 30 mm (n=100) diameter of the ring, 20-60 mm intrauterine tandem with an angel of 60˚. The absorbed doses and volumes were defined according to ICRU 38 (30-32). The reference dose (6 Gy per fraction) was specified as a minimum dose to the surface of the target volume. The target volume (CTV_B) was equal with the gross tumor volume (GTV) at start of radiotherapy. In case of more advanced tumors a new tumor

Table II. Prior and concurrent diseases and history of prior surgery.

	Number	Percent
Diseases		
Cardiovascular	51	38.9
Diabetes	11	8.4
Gastrointestinal	14	10.7
Gynecological	6	4.6
Other	50	38.2
Type of prior surgery		
Gastrointestinal	43	32.8
Urological	1	0.8
Gynecological	24	18.3
Other	35	26.7

evaluation (examination under anesthesia and pelvic CT) was done after 45-50 Gy of external dose for dose planning purposes of the brachytherapy boost. The shrunken gross tumor volume (GTV) was then set equal to the clinical target volume (CTV_B) of brachytherapy. Point doses in point A and B, at the bladder reference point (BRP), and at the rectal reference points were also calculated. Orthogonal X-rays (A-P and lateral) were taken at every treatment session. A bladder catheter with 7-cc contrast medium in the balloon was used when defining the bladder reference point.

The brachytherapy sessions were given once a week in parallel with the external beam therapy. In 91 patients (70%) five fractions (30 Gy; EQD_2=40 Gy) were given and in 40 patients (30%) three fractions (18 Gy; EQD_2=24 Gy) were administered. On the brachytherapy day both an external and an intracavitary fraction was given with a minimum of 6 h apart. In case of smaller tumors in stages IB, IIA and early IIB five fractions of 6 Gy each were given (total EQD_2=90 Gy for α/β=10), and in cases with more advanced tumors (late IIB, III, IV) three fractions of 6 Gy were given in parallel with 60 Gy of external beam therapy (total EQD_2=84 Gy for α/β=10). A CT-based 3-D dose planning system was used for external beam therapy (TMS, Helax AB, Uppsala, Sweden) and for brachytherapy planning (NPS and PLATO, Nucletron Int. B.V.). During the last three years, MRI of the pelvis has been added to the imaging technique used to define the target volume.

Concomitant chemotherapy was used since the year 2000 in 47 patients (36%) of this series. The agent used was single drug cisplatin 40 mg/m^2 given weekly in parallel with the radiotherapy. Median number of courses was 5 (range: 1-6). Hematology and serum chemistry were regularly checked out once a week.

All patients were followed-up during the first 5 years at the Department of Gynecological Oncology, Örebro. The first visit was 1 month after the end of radiotherapy, then every 3 months during the first year, every 4 months during the second and third year, every 6 months up to 5 years and then annually up to 10 years. No patients were lost to follow-up. The mean follow-up time of patients alive was 63 months (range: 7-169 months). Special attention was paid to early and late tissue reactions as well as primary cure of the tumor or recurrences. The follow-up data were stored in a regional quality register at the Department of Gynecological Oncology.

In the statistical analyses the Pearson Chi-square, the t-test, ANOVA statistics, logistic regression analysis, Kaplan-Meier technique for survival analysis, the log-rank test, the Gehan's Wilcoxon test and the Cox analysis were used. $P<0.05$ (two-sided test) was regarded as statistically significant. The Statistica (version 7.1, 2005) software package (StatSoft, Inc., Tulsa, OK, USA) and the SPSS (version 15.0.0, 2006) package (SPSS Inc., Chicago, IL, USA) were used in the statistical analyses.

Results

The mean age of the patients in the complete series (n=131) was 65.3 years (28-90 years). One hundred and seven tumors were squamous cell carcinomas (82%), and most tumors were moderately well or poorly differentiated (Table I). HPV-status was known for 37 tumors and of those 26 cases (70%) were positive for HPV-DNA. One hundred and three tumors were graded according to a morphological grading system (Stendahl-Willén). The mean malignancy score was 15.4 (9-21). The mean value of tumor depth was 38 mm, of tumor width 44 mm, and of tumor length 34 mm. Prior diseases or concurrent diseases and surgery are presented in Table II.

All tumors in this series were treated with a combination of pelvic external beam therapy and intraluminal brachytherapy using a ring applicator set. In 47 patients (36%) concomitant chemotherapy (chemoradiotherapy) was given.

After completion of the primary radiotherapy or chemo-radiotherapy 121 out of 131 tumors (92%) were primarily cured (complete remission). The age of the patients was not a predictive factor (t-test; P=0.667). The mean hemoglobin value was significantly (t-test; P=0.049) higher at start of radio-therapy for those patients with local tumor control compared with those with residual tumor after radiotherapy. In the group with radiotherapy alone (n=84) the cure rate was 89% and in the chemoradiotherapy group (n=47) it was 98% (Pearson Chi-square; P=0.076). The primary cure rate was significantly (Pearson Chi-square; P=0.007) associated with tumor stage and varied from 100% in stage I to 60% in stage IV (Table III). Squamous cell carcinomas were primarily cured in 96%, adenocarcinomas in 81%, and adenosquamous carcinomas in only 33% (Pearson Chi-square; P=0.00003). Tumor grade was also significantly (Pearson Chi-square; P=0.00002) associated with primary cure rate. Well differentiated carcinomas did worse than moderately well and poorly differentiated carcinomas. DNA ploidy of the tumor was not associated with primary cure rate. The malignancy grading score was not significantly (t-test; P=0.196) associated with primary cure of the tumor. Tumor size, measured as depth (t-test; P=0.012), width (t-test; P=0.003), and length (t-test; P=0.0007), was highly significantly associated with primary cure rate.

A number of treatment related parameters were associated with the probability of primary tumor control. The anterior-posterior measurement of the patient in the level of pelvis, the absorbed brachytherapy dose, the 2-Gy equivalent (EQD_2) brachytherapy dose, total 2-Gy equivalent (EQD_2) external

Table III. Radiotherapy parameters versus primary tumor cure in the complete series.

Parameter	Primary cure Mean	Residual tumor Mean	T-test P-value
Total brachytherapy dose	26.5 Gy	22.8 Gy	0.045
Total brachytherapy dose (EQD_2[a])	35.3 Gy	30.4 Gy	0.045
Total dose (EQD_2[a])	88.1 Gy	80.0 Gy	0.00002
Interruption of radiotherapy[b]	1.2 days	4.3 days	0.030

[a]Equivalent dose of 2 Gy fractions (α/ß=10), [b]External beam radiotherapy.

Table IV. Type and sites of tumor recurrences.

Site	Number	Percent
Local	4	3.1
Regional	7	5.3
Distant	17	13.0
Local + regional	3	2.3
Local + distant	2	1.5
Regional + distant	6	4.6
Local ± other	9	6.9
Regional ± other	16	12.2
Local or regional	22	16.8
Distant ± other	25	19.1

plus brachytherapy dose, and the number of days of interruption (delay) of external irradiation were all significant predictive factors (Table III).

In the complete series 39 tumor recurrences (30%) were recorded at the time of the last follow-up. In 22 cases the recurrences were local or regional (17%), and in 17 cases distant metastases (13%) (Table IV). The age was not a predictive factor of tumor recurrence (t-test; P=0.304). Patients with tumor recurrences were significantly (t-test; P=0.017) heavier (mean: 74.9 kg) than patients with no evidence of disease (mean: 68.8 kg). The mean hemoglobin value at start of radiotherapy was similar (t-test; P=0.922) for the two groups. The recurrence rate was significantly (Pearson Chi-square; P=0.047) lower for patients treated with chemoradiotherapy (19%) compared with patients treated with radiotherapy alone (36%). FIGO stage was significantly (Pearson Chi-square; P=0.012) associated with the recurrence rate.

In stages I and II the recurrence was similar (20-30%), but in stages III and IV substantially higher (40-60%). Adenocarcinomas showed a significantly (Pearson Chi-square; P=0.0008) higher recurrence rate (52%) than squamous cell carcinomas (23%) in this series. The adenosquamous carcinomas were few (n=3), but all of these tumors recurred. Among nine well differentiated carcinomas no recurrences were recorded, but for moderately well differentiated and poorly differentiated carcinomas the recurrence rate was similar (32% versus 30%). Tumors with an aneuploid DNA-profile had a significantly (Pearson Chi-square; P=0.039) higher recurrence rate (40%) than tumors with a diploid profile (22%). Among eight tetraploid tumors only one recurrence was noted. HPV-status of 37 evaluable tumors was not significantly associated with tumor recurrence rate. In this series of tumors the malignancy grading score was similar for recurring (mean: 15.7) and non-recurring (mean 15.3) tumors (t-test; P=0.512). Tumor size, measured as depth (t-test; P=0.103), width (t-test; P=0.080), and length (t-test; P=0.772), was slightly higher, but not statistically significant, in the group with recurrent tumors.

A number of treatment related parameters were associated with the probability of tumor recurrence. The anterior-posterior measurement of the patient in the level of pelvis, total brachytherapy dose, total 2-Gy equivalent brachytherapy dose, total 2-Gy equivalent external plus brachytherapy dose, and number of fractions given by brachytherapy were significant predictive factors (Table V).

Table V. Radiotherapy parameters versus tumor recurrences in the complete series.

Parameter	No recurrence Mean	Recurrence Mean	T-test P-value
Total brachytherapy dose	27.1 Gy	23.9 Gy	0.002
Total brachytherapy dose (EQD_2[a])	36.2 Gy	31.9 Gy	0.002
Total dose (EQD_2[a])	88.2 Gy	86.1 Gy	0.067
Number of brachytherapy fractions	4.5	4.0	0.003

[a]Equivalent dose of 2 Gy fractions (α/ß=10).

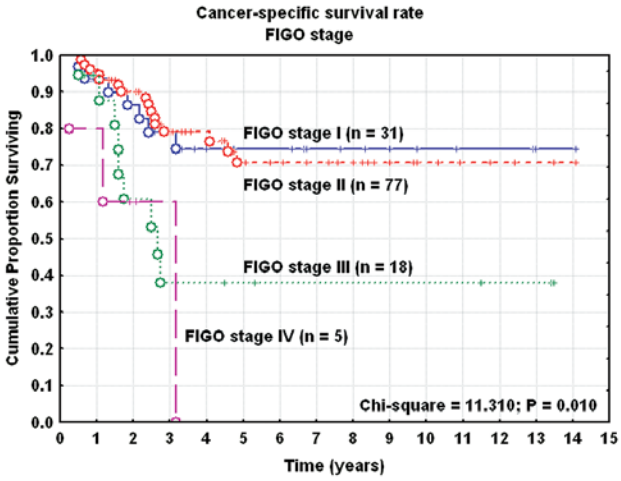

Figure 1. Cancer-specific survival rate versus FIGO-stage in the complete series.

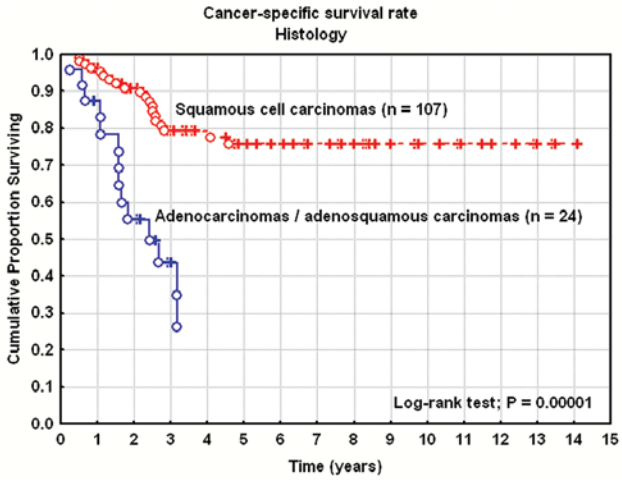

Figure 2. Cancer-specific survival rate versus tumor histology in the complete series.

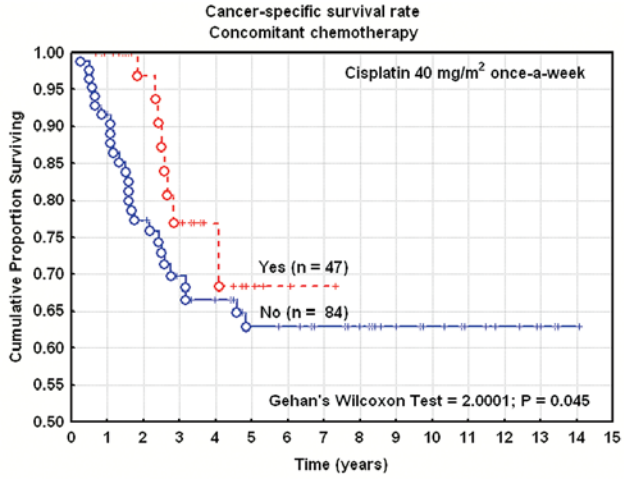

Figure 3. Cancer-specific survival rate versus concomitant chemotherapy (Yes) or radiotherapy alone (No).

Table VI. Early and late radiation reactions (RTOG/EORTC)[a] of the complete series.

	Number	Percent
Early reactions		
Diarrhea (grade 1)	72	55.0
Diarrhea with blood (grade 2)	1	0.8
Dysuria	3	2.3
Total	76	58.0
Late reactions		
Diarrhea (grade 1)	28	21.4
Diarrhea with blood (grade 2)	24	18.3
Intestinal obstruction (grade 3)	6	4.6
Intestinal fistula (grade 4)	8	6.1
Dysuria (grade 1)	14	10.7
Hematuria (grade 2)	6	4.6
Bladder fistula (grade 3)	4	3.1
Intestinal or bladder fistula	8	6.1
Serious (grade 3 or 4) late reactions	14	10.7
Total	66	50.4

[a](RTOG/EORTC) (42).

The overall 5-year survival rate of the complete series was 50% and the 5-year cancer-specific survival rate 65%. The cancer-specific survival was similar in FIGO stages I (74%) and II (71%). In FIGO stage III 38% of the patients survived 5 years, but none in stage IV (Fig. 1). Tumor size was a strong prognostic factor for cancer-specific survival rate. Tumor width was the most important single measurement (Cox analysis; P=0.00007) and the only independent and significant one in a Cox multivariate analysis including tumor length, width and thickness. Squamous cell carcinomas had a much better prognosis than adenocarcinomas and adenosquamous carcinomas (Fig. 2). This was also true after correction for differences in tumor stage distribution. Tumor grade was not significantly (Chi-square; P=0.817) associated with the cancer-specific survival rate. Aneuploid tumors had a slightly worse prognosis than diploid tumors with a 10% lower (57% versus 67%) 5-year cancer-specific survival rate (Gehan's Wilcoxon test; P=0.091). The malignancy grading score was not significantly (log-rank test; P=0.857) associated with the cancer-specific survival rate. This was also confirmed in a Cox regression analysis (P=0.404). Patients receiving concomitant chemotherapy (n=47) had a significant (Gehan's Wilcoxon test; P=0.045) improvement in cancer-specific survival rate (Fig. 3). The benefit of concomitant chemotherapy was similar for squamous cell carcinomas and for adenocarcinomas.

Early radiation reactions were recorded in 76 out of 131 patients (58%). Most reactions were of grade 1, diarrhea and/or dysuria. In one patient bloody stool was noted. Late radiation reactions were recorded in 66 patients (50%). Slight radiation reactions (grade 1) were noted in 29 patients (22%),

medium reactions (grade 2) in 23 patients (18%), and severe late reactions (grades 3 and 4) in 14 patients (11%) (Table VI).

Discussion

Cancer of the uterine cervix is the second most common malignancy in women worldwide and number one in some developing countries (2). The mortality rate is also rather high and >270,000 women will die annually of cervical cancer. In the Western world screening programs have significantly lowered the incidence and moved cervix cancer out of the top 10 list of female malignancies (33). Both surgery (early stages) and radiotherapy (advanced stages) are important treatment options. Meta-analyses have confirmed survival advantage of chemoradiotherapy over radiotherapy alone in FIGO stages IB2-IVA (5). Cisplatin-based chemoradiotherapy is now standard at most centers and it was rapidly incorporated in the treatment schedules after the NCI clinical alert 1999 (34).

External beam pelvic irradiation and intraluminal cervical brachytherapy is the standard radiotherapy technique in most advanced cases (4). Brachytherapy alone is sometimes used in early stage I disease and as preoperative radiotherapy before Wertheim-Meigs surgery (35). Brachytherapy plays a major role in treatment of cervical cancer in all stages and is a prerequisite for an optimal treatment of the central part of the pelvis. The steep dose-gradient allows a very high central dose and the rapid fall off of the irradiation will protect the risk organs from unacceptable high doses (7). Accurate definition of the clinical tumor volume (CTV) and the risk organs (bladder and rectum) are extremely important to optimize the brachytherapy part of the complete radiotherapy treatment in cervical carcinoma. The timing of the brachytherapy insertions during or after the external beam therapy is also important (18). From a radiobiological point of view the number of fractions and the size of the individual fractions are of importance, especially for late tissue reactions. To improve local tumor control and to minimize late tissue reactions in the risk organs image-guided treatment planning using both CT and MRI has been described and advocated (26-28). This new technique is very time- and resource-consuming compared with earlier used standard techniques.

In the present study, covering the time period 1992-2006, a standardized technique was used where MRI was not routinely part of the dose planning. The planning was performed from data achieved after examination under anesthesia, ultrasound, and CT scans with the cervical ring applicator *in situ* (13-15). The delineation of the tumor borders are less accurate with this technique compared with image-guided technique using MRI with the applicator *in situ*. Before switching over to this new and resource consuming technique the results with regard to local tumor control, recurrences, survival and late tissue reactions were evaluated with a technique using CT alone in the dose-planning process.

In this series 121 out of 131 tumors (92%) were primarily cured. The majority of the tumors were in stage II (59%). Tumor stage was significantly associated with the primary cure rate. In the group treated with chemoradiotherapy the cure rate was 98%. The importance of concurrent chemotherapy (weekly cisplatin) was also shown in this series.

Adenocarcinomas did worse in this series compared with squamous cell carcinomas. DNA ploidy and the malignancy grading score were not significantly associated with primary cure rate. This was in contrast to our earlier findings in surgically treated early stage cervical carcinomas where the malignancy grading system was a highly significant prognostic factor (36). As reported in other studies the hemoglobin value at start of therapy was a predictive factor for local tumor control (37). Tumor size was shown to be one of the most important predictive factors for tumor control in this series as well as in others (36). The importance of brachytherapy was shown by improved local control with increased number of brachytherapy fractions as well as increased brachytherapy dose and the total 2-Gy equivalent brachytherapy dose. Total external dose was also of importance as well as absence of interruption and delay of the external therapy (38).

Tumor recurrences were significantly associated with stage, type of histology and aneuploid DNA profile. Non-significant factors were age, hemoglobin value, the malignancy grading score, HPV-status and tumor size. Once again, the number of brachytherapy fractions and the brachytherapy dose were significant predictive factors.

The 5-year survival rate of this series was 50%. This was a mixed series of stage I-IV tumors all suitable for combined external and intracavitary treatment. Thus, this was a selected series of advanced and less advanced cervical carcinomas. In stage I the tumors were not suitable for surgery and in stages III-IV still technically suitable for brachytherapy. In stage II the 5-year survival rate was 71%. Tumor size was the strongest and only independent prognostic factor for survival in multivariate analysis. Squamous cell carcinomas had a much better prognosis than adenocarcinomas and adenosquamous carcinomas in this series. Chemoradiotherapy significantly improved survival and this was true for all histological subtypes of cervical carcinomas. Tumor grade, DNA-ploidy and the malignancy grading score did not significantly influence the survival probability.

Radiation reactions were rather frequent in this series. However, most early reactions were grade 1 and of limited clinical significance. In 23 patients (18%) grade 2 late reactions and in 14 patients (11%) grade 3-4 late reactions were recorded. These frequencies of late tissue reactions are higher than those reported in modern series where 3-D image-guided dose-planning using MRI-technique is used (39). Improved local tumor control has been reported for tumors >5 cm (39). However, local tumor control rate, stage by stage, seems to be similar in our series and series published during recent years using the new dose-planning technique.

Brachytherapy seems to be an important part of the irradiation technique for cervical carcinomas in stages I-IV. Local tumor control can be improved and the risk of early recurrences reduced compared with external beam therapy alone. The improved accuracy of the brachytherapy technique achieved by using a 3-D image-guided dose-planning seems to reduce radiation side effects but with unchanged or in certain cases improved tumor control rate (40). Since smaller tissue volumes are irradiated with this technique it is obviously a clinically significant improvement in brachytherapy with

regard to the risk of unwanted tissue reactions (41), but at the cost of substantially increased resources of time and personnel.

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