Radiation therapy in cervical carcinoma fifteen years experience in a Norwegian health region

E. Lorenz[1], T. Strickert[2], B. Hagen[1]

[1]Department of Gynaecological Oncology and [2]Department of Oncology and Radiotherapy, St. Olavs Hospital/University Hospital, Trondheim (Norway)

Summary

Background: To study the treatment of patients with cervical carcinoma with regard to side effects and survival. *Materials and Methods:* A retrospective analysis of 107 patients with cervical carcinoma treated by radiotherapy with curative intent between January 1, 1987 and December 31, 2001. *Results:* Median follow-up: 139 months for surviving patients and 23 months for deceased patients. Five-year overall and disease-specific survival for all stages was 36% and 45%, respectively. Corresponding figures for each stage were, Stage I: 54% and 80%, Stage II: 41% and 56%, Stage III: 33% and 36% and Stage IV: < 1%. Five-year actuarial incidence of late reactions, all grades were: vagina 77%, rectum 41%, urinary tract 28%, and gastrointestinal tract 37%. *Interpretation:* a great variation of treatment techniques resulted in an overall survival somewhat inferior to that in other comparable series. Over time, an increasing tendency to include brachytherapy and external tumour boost was observed.

Key words: Cervical carcinoma; Radiation therapy; Late reactions; Survival.

Introduction

In accordance with Norwegian general health policy, hospital-based cancer care was regionalised during the 1980s. The organization of care for gynaecologic cancer patients was transferred from one centralised institution covering the whole country (i.e., the Norwegian Radium Hospital) to four regional gynaecological oncology units. Our institution was established in 1987 as the centre of hospital-based gynaecological cancer care for three Norwegian counties with a population of 630,000 inhabitants.

Since that time, almost all women with cervical carcinoma in this area have been treated at this institution.

Radiation therapy has been managed by the gynaecolgical oncologists in cooperation with the physicists and radiation therapists at the Department of Oncology and Radiotherapy.

The aim of this retrospective study was to analyse the outcome in patients treated by primary radiation therapy with curative intent from 1987 until 2001.

Material and Methods

From January 1, 1987 until December 31, 2001, 408 women were diagnosed with cervical cancer and 360 patients were treated with curative intent. One hundred and seven had definitive radiotherapy while 253 had primary surgery followed by adjuvant radiation therapy in 77. The clinical records and radiotherapy journals of all patients were reviewed. The data were checked with the electronic radiation therapy registry (VISIR). When follow-up was done at local hospitals or by general practitioners, information was retrieved from these sources. There were 107 women who had definitive radiation therapy with curative intent who formed the study group.

The study was approved by the regional research ethics committee.

Revised manuscript accepted for publication May 12, 2008

Median age was 64 years (range 29-88 years). Sixteen percent of the patients were nulliparous, 60% had 1-3 and 21% > 3 deliveries; missing data resulted in 3%. Thirty-seven percent were smokers, 22% did not smoke when diagnosed, however, data on smoking habits were missing in 40% of the cases. The median BMI was 23 (range 16-45), based on available data from 88/107 patients. The WHO performance status was 0 in 60%, one in 33% and two in 5% of the patients.

Staging was done by FIGO guidelines, based on findings at gynaecologic examination under general anaesthesia, cystoscopy, and chest X-rays. Evaluation by CT and MRI has been used since 2000 and the results have influenced treatment but not stage assignment. Surgical evaluation was not done in these patients. The stage distribution is shown in Table 1.

Ninety-six women (90%) had squamous cell carcinoma, seven (6%) had adeno- or adenosquamous carcinoma and four women (4%) had other histology.

Therapy

The treatment combinations used are shown in Table 2. In spite of the variety of combinations, certain trends could be observed. In 1987, external radiation was mainly delivered by two opposed standard fields. An exception was The Scandinavian Multicenter Study [1] into which 13 patients with FIGO Stages IIIB and IV were included between March 1989 and December 1992. They received external radiation by a four-field standard box with a total dose of 64.8 Gy (1.8 Gy x 36.5 fractions/ week). No intracavitary treatment was given. Half the group was randomized to receive neoadjuvant chemotherapy (cisplatinum 100 mg/m^2/day combined with 5FU 1000 mg/m^2/24 hrs for 96 hrs; every 3 weeks for 3 courses). Since October 1993, treating patients exclusively by external radiation therapy has been uncommon.

From 1994, patients with FIGO Stage IB-IVA have been treated according to the Nordic Protocol for Cervical Carcinoma (NOCECA) applying two opposed standard fields ap/pa with an additional boost given by two lateral fields with treatment planning based on CT images. The total dose to the pelvis

Table 1. — *Stage distribution.*

Stage	Number of patients	Percentage (%)
IA	1	0.9
IB	4	3.7
IIA	5	4.7
IIB	37	34.6
IIIA	10	9.3
IIIB	41	38.3
IVA	8	7.5
IVB	1	0.9

Table 2. — *Treatment overview.*

Treatment	IA	IB	IB1	IB2	IIA	IIB	IIIA	IIIB	IVA	IVB	Total
ap/pa field						5		11	1		17
ap/pa field + neoadjuvant chemotherapy		1				1		1	1	1*	4
ap/pa field + brachytherapy					3	9	4	5			22#
ap/pa field + brachytherapy + neoadjuvant chemotherapy							2				2
4-field box						1	5				6¶
4-field box + neoadjuvant chemotherapy							6	1			7¶
4-field box + boost + weekly cisplatin						1					1
4-field box + brachytherapy					1	1	2†				4
ap/pa field + boost by 2 lat fields						1		1	3		5**
ap/pa field + boost by 2 lat fields + brachytherapy		1	1	1	1	20* ‡, §	2	10 §	2		38**
brachytherapy only	1										1
Total	1	2	1	1	5	37	10	41	8	1	107

* 1 patient with additional paraaortic fields; † 1 patient with boost, paraaortic fields, and inguinal fields; ‡ 1 patient with neoadjuvant chemotherapy; § 1 patient with cisplatin weekly; # includes 9 patients with central shielding after half of the external radiation and the whole of the intracavitary treatment had been given, absorbing 1/3 of the dose. Abandoned in october 1989; ¶ Scandinavian Multicenter Study from March 1989 until December 1992; ** radiation therapy according to NOCECA guidelines.

was 45 Gy (1.8 Gy x 25; 5 fractions/week). Total tumour dose (boost) depended on tumour size. For intracavitary treatment, dose prescription had to be made to point A [2] while fractionation and total dose were left to the discretion of the participating departments. Patients not suited for intracavitary treatment were to receive 50.4 Gy to the pelvis and 80 Gy to the tumour by external irradiation only (unpublished results). All 43 patients were treated according to this protocol and 32 were included in the study proper. Two of these patients also participated in a feasibility study where cisplatinum 40 mg/m^2/week was given concurrently [3]. Fractionation ranged from 1.8-2 Gy/fraction and total dose to the pelvis from 40-65 Gy with additional boost doses from 10-30 Gy. External irradition was given by linear accelerator, mainly with 15 MV photons.

Four patients were sent to the Norwegian Radium Hospital for radium brachytherapy. Since autumn 1988, a Selectron HDR afterloading machine with a train of 20 ^{60}Co sources with an initial total activity of approximately 360 GBq was available at our own institution.

In 1996 it was replaced by a GammaMed 12i HDR by a ^{192}Ir stepping source with a starting activity of 400 GBq. The Fletcher-Suit-Delclos applicator was most often used, but in certain anatomical findings a tandem applicator was deemed more suitable.

Dosage and fractionation for intracavitary treatment varied from 9 Gy x 2 to 5.5 Gy x 2-3 to 5 Gy x 4. The timing of brachytherapy was aimed at exploiting tumour shrinkage due to external irradiation. For practical reasons, such as long waiting time for external treatment, some patients had to start with the intracavitary therapy. Brachytherapy and external radiation were given on separate days. If intracavitary treatment was given after the completion of external treatment, it was commonly given with 72 hours intervals. Standard plans for brachytherapy were used based on orthogonal images of the applicator. In-vivo dosimetry at the level of the bladder and rectum was not performed.

Neoadjuvant chemotherapy was given to 15 patients in all, of whom seven were included in the Scandinavian Multicenter Study. The eight remaining women had various regimes containing cisplatinum and 5FU.

Concomitant chemotherapy with Cisplatinum 40 mg/m^2/week has been standard treatment since 2000 provided the patient could tolerate combined therapy.

Follow-up

Early side-effects were scored according to the RTOG-EORTC acute radiation morbidity scoring scheme for upper and lower gastrointestinal tract, urinary tract and skin [4].

After completing treatment, patients were offered follow-up visits every three months for two years, twice every year up to four to five years and once a year therafter. The visits comprised patient history and gynaecological examination. Chest X-ray was done twice during the first year and therafter, once every year. Additional examinations were done on indication.

Assessment of late side-effects started three months after completed treatment according to the RTOG-EORTC late radiation morbidity scoring scheme [4]. Lymph edema was registered as absent or present, and if present, registered as demanding treatment or not.

Microfractures verified by MRI were recorded as absent or present, and the grading of ureteral stenosis and pelvic pain (without microfractures) was done according to the Common Toxicity Criteria Scale, version 2.0 [5]. Complications attributable to verified disease recurrence were not scored as symptoms related to treatment side-effects.

Statistical methods

For statistical analysis SPSS 13.0 for Windows was used. For paired samples a t-test was used for paired data and Spearmans' range coefficient for non-parametric data. Actuarial estimates for survival and risk of late reactions were calculated using the Kaplan-Meier product-limit methods. A log-rank test was used for comparison of survival distributions between different stages.

Results

Follow-up time for surviving patients ranged from 73- 230 months (median 139), and for deceased patients from 2-198 months (median 23). No patients were lost to follow-up.

The biologically effective dose (BED) was estimated with $\alpha/\beta = 10$ for tumour response and early tissue reactions and $\alpha/\beta = 3$ for late tissue reactions [6, 7]. BED10 to point A as

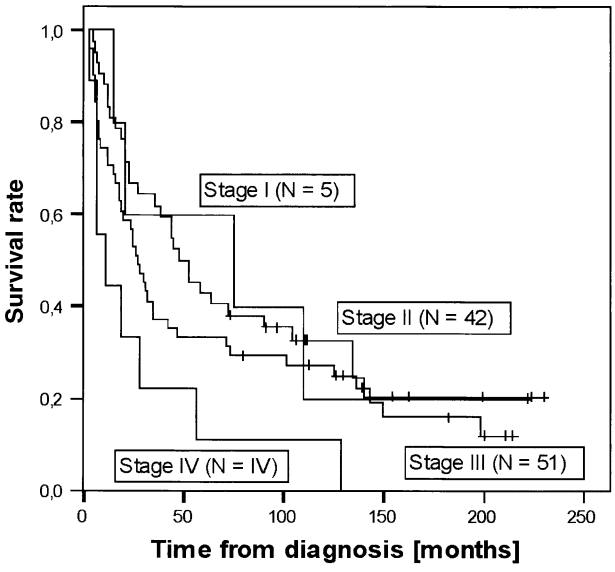

Figure 1. — Overall survival.

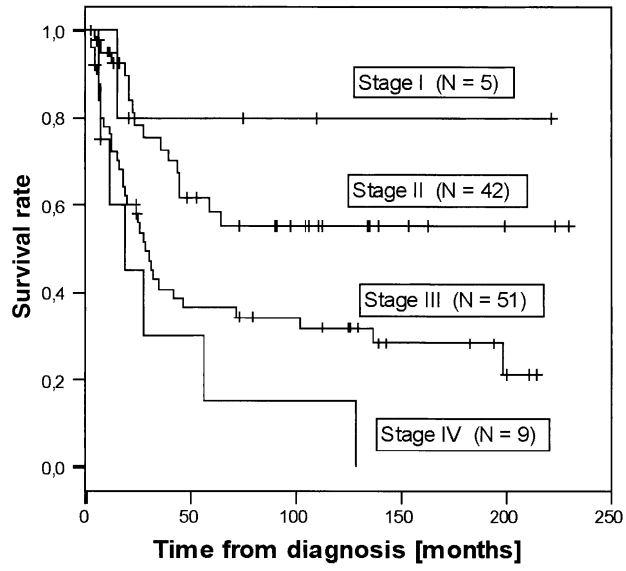

Figure 2. — Disease-free survival.

a sum of the total doses of both external and intracavitary treatment, showed a mean value of 80 Gy10 and a median value of 77 Gy10. BED3: as dose to organs at risk was not measured, total dose to point A was taken as an approximation, mean value of 118 Gy3 and median value of 115 Gy3.

The median total treatment time was 41 days (range 37-64 days) for patients treated with a combination of external radiotherapy of 50 Gy total dose and intracavitary treatment according to the NOCECA protocol. For patients who did not receive brachytherapy or who were treated according to other protocols, the median total treatment time was 45 days (range 25-68 days).

At the end of the observation time, 86 of 107 patients had died, 56 of disease while 27 patients had died of other causes, two of whom had a known relapse of cervical carcinoma. Three women died of treatment complications: one patient died about two months after completed treatment due to intestinal obstruction and colon perforation, the second patient had a verified relapse and died of aspiration after general anaesthesia, while the third died of Listeria meningitis after palliative irradiation for cerebral metastases.

Overall and disease-specific survival by FIGO stage are shown in Figures 1 and 2.

For the whole group, 5-year overall and disease-free survival was 36% and 45%, respectively. The corresponding figures for each stage were: Stage I 54% and 80%, Stage II 41% and 56%, Stage III 33% and 36%, and Stage IV < 1%.

Tumour stage was a significant variable for disease-free survival ($p = 0.003$).

In all, 57 patients had a relapse and 79% of these occurred during the first two years after completed treatment. There were equal numbers for the site of recurrence within and outside the radiation field with 21 patients (36.8%) in each group. Fourteen patients (24.6%) relapsed both inside and outside the radiation field. The localization of the relapse remained unknown for one patient. Treatment of recurrences was individualized and most often given with palliative intent. Two patients were alive without evidence of disease following treatment of relapse (Figure 3).

Radiation side-effects

Early tissue reactions are shown in Table 3. There was no correlation between BED10 and risk of early tissue reactions (data not shown). Late tissue reactions are shown in Table 4. Most were registered during the first 20 months. No new side-effects were seen after 60 months. In addition to the numbers shown in Table 4, four women had pelvic microfractures verified by MRI, and four developed lymph edema, three of whom received lymph drainage therapy.

The 5-year actuarial incidence of late reactions for all grades was: vagina 77%, rectum 41%, urinary tract 28%, and gastrointestinal tract 37%.

Table 3. — *Early tissue reactions.*

	Grade 1 + 2	Grade 3	Grade 4
Upper GI tract	47	3	0
Lower GI tract	80	4	1
Urinary tract	13	2	0
Skin	15	0	0

Table 4. — *Late tissue reactions.*

	Grade 1 + 2	Grade 3	Grade 4
GI tract	28	2	1
Rectum	31	2	0
Urinary tract	9	1	3
Vagina	59	0	0
Pelvic pain	10	0	0

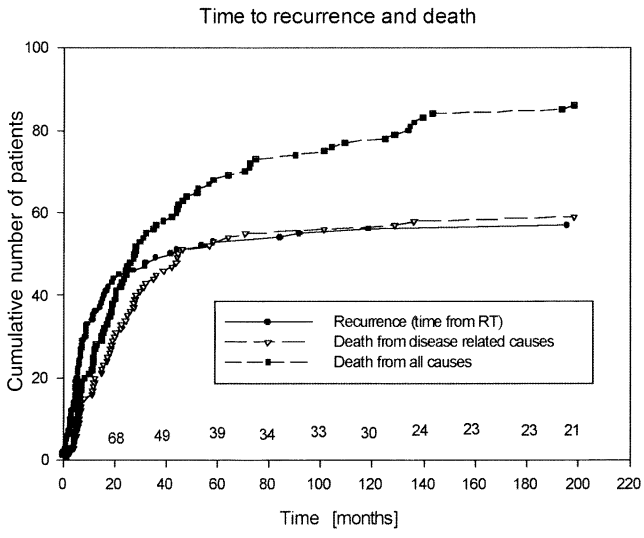

Figure 3. — Time to recurrence and death cumulative number of patients with death from all causes and death from disease-related causes from diagnosis to death. Also shown is the cumulative number of recurring patients from end of RT. The number of patients at risk at every 20-month interval is shown at the bottom of the panel.

Discussion

This is a retrospective analysis from a relatively small treatment center but covering quite a long period of time. This consequently posed certain difficulties in that the principles of both diagnosis and treatment changed over time.When analysing data according to patient characteristics, prognostic factors, and mode of treatment in order to achieve homogeneous groups, numbers were small. Thus comparison was difficult and calculation of statistical significance often meaningless. Clinical records often lacked basic information, such as for 40% of the patients on smoking habits and for about 53% on tumour size. During follow-up visits, there was no systematic use of a scoring system and to a large degree, registration of side-effects depended on the individual doctor and patient. The consequences are well known and described in the literature [8].

We graded early and late side-effects retrospectively acording to the RTOG/EORTC scoring system [4] as far as this was feasible. For some side-effects we used NCI/CTCv2.0 [5]. A strength of the study is that it was population-based with almost no referral to other institutions and included all women treated with curative intent.

A study by Wang *et al.* [9] from Taiwan of 173 patients showed a 5-year overall survival of 58% for all stages (79% for IB + IIA, 59% for IIB + IIIA, 41% for IIIB + IVA). For 189 patients, Pötter *et al.* [10] reported a 3-year disease-specific survival of 68.6% for the whole group (100% for IA, 77.1% for IB, 100% for IIA, 78% for IIB, 52.1% for IIIA, 58.6% for IIIB, 53.3% for IVA and 0% for IVB). Recently published results by Yamashita *et al.* [11] showed a 5-year disease-specific survival of 68.7% for IIB, 54.5% for III and 28.6% for IVA. In a second study in 2007, Pötter *et al.* [12] reported a 3-year disease-specific survival of 68% for all stages with 84.6% in IB, 83.4% in IIA, 61.4% in IIB, 50% in IIIA, 42.2% in IIIB and 28.6% in IVA. In comparison, our survival data are inferior which might be due to several reasons. Firstly, our material was unselected and all women who started treatment with curative intent were included. Secondly, until 2000, the clinical work-up before treatment included neither CT nor MRI. Thus even macroscopic metastases to lymph nodes or intraabdominally would potentially not have been detected and not properly treated. A third aspect is the treatment itself, which for 34 patients was given without any kind of tumour boost – external or intracavitary – and with neoadjuvant chemotherapy only for some. Numbers not shown here support the knowledge that a combination of external and intracavitary treatment leads to improved disease-specific survival and therefore should always be aimed at. On the other hand, one should have in mind that there is a correlation between lower tumour stage and the successful use of brachytherapy since the anatomy in locally advanced cervical carcinoma can render the insertion of an applicator impossible.

The pattern of relapse showed equal numbers of recurrence inside and outside the former radiation fields and differed from other studies reporting higher frequency of relapse outside formerly irradiated areas [10, 12, 13]. The radiation therapy used was likely not to have sufficed for local tumour control because of a too low total dose and the lack of brachytherapy equipment allowing individual tailoring of the treatment. It was not possible to show any trend in treatment results over time due to small numbers.

Registration of side-effects after radiation therapy is often regarded as insufficient and subject to methodical flaws, which has been the issue for an ongoing discussion for many years. Developing a scoring system which both confers an accurate picture of the changes over time and is feasible in clincal practice is difficult. Several scoring systems are in use such as RTOG/EORTC [4], LENT/SOMA [14] – partly with modifications – and revised versions of NCI/CTC [5, 15, 16]. Data collected by different scoring systems can not be directly compared [17-19]. Currently, there is an increasing agreement that an actuarial estimate of incidence is the most appropriate way to handle data on side-effects [20-22].

These data showed higher complication frequencies compared to more recent treatment results, but did not differ that much from data in older treatment series [9, 10, 12, 13]. Logsdon *et al.* [13] discussed the correlation between total external dose and a rising number of late complications. Pötter *et al.* [12] were able to show in their series that the complication rates dropped as the result of individualized treatment and the use 3D-based brachytherapy.

Development since 2001:

At our department, all external irradiation is now delivered by individually shaped fields in accordance with the findings on CT and MRI and planning on CT slices. In brachytherapy, MRI is done for every insertion which

allows appropriate delineation of both tumour volume and organs at risk (OAR) enabling us to prescribe the doses to the tumour volume instead of point A [23,24]. New software allows individualized brachytherapy planning. The aim is to implement the GEC-ESTRO recommendations [25, 26] for brachytherapy and IMRT for external radiation in order to give high radiation doses to the tumour and at the same time, reduce the radiation to OAR and consequently, the risk of tissue reactions [27-29].

Conclusion

A variety of treatment combinations were used during the years 1987-2001. Results in terms of survival and late tissue reactions were somewhat inferior compared to other series. The treatment has been modernised in all aspects since 2001. Hopefully this will result in a better survival with fewer late tissue reactions.

References

[1] Sundfør K., Tropé C.G., Høgberg T., Onsrud M., Koern J., Simonsen E. *et al.*: "Radiotherapy and neoadjuvant chemotherapy for cervical carcinoma". *Cancer,* 1996, *77,* 2371.

[2] ICRU Report 38: "Dose and volume specification for reporting intracavitary therapy in gynecology". Bethesda, MD: International Commission on Radiation Units and Measurements, 1985.

[3] Lindegaard J.C., Mirza M.R., Lorenz E., Lundqvist E.A.: "A Nordic feasibility study of accelerated radiotherapy and concomitant cisplatin in the treatment of advanced cervical cancer stage IIB – IVA (NSGO-CC-9901)". *Radiother. Oncol.,* 2002, *64* (suppl. 1), 49.

[4] Cox J.D., Stetz J., Pajak T.F.: "Toxicity Criteria Of The Radiation Therapy Oncology Group (RTOG) And The European Organization For Research And Treatment Of Cancer (EORTC)". *Int. J. Radiat. Oncol. Biol. Phys.,* 1995, *31,* 1341.

[5] The Revised Common Toxicity Criteria: Version 2.0 CTEP website http://ctep.cancer.gov/forms/CTCv20_4-30-992.pdf.

[6] Fowler J.F.: "The linear-quadratic formula and progress in fractionated radiotherapy". *Br. J. Radiol.,* 1989, *62,* 679.

[7] Joiner M.C., van der Kogel A.J.: "The linear quadratic approach to fractionation and calculation of isoeffect relationships". In: Steel G.G. (ed.) Basic Clinical Radiobiology. 2nd edition, London, Arnold, 1997, 106.

[8] Bent S., Padula A., Avins A.L.: "Brief communication: better ways to question patients about adverse medical events". *Ann. Intern. Med.*, 2006, *144,* 257.

[9] Wang C.J., Leung S.W., Chen H.C., Sun L.M., Fang F.M., Changchien C.C. *et al.*: "High-dose rate intracavitary brachytherapy (HDR-IC)". In: "Treatment of Cervical Carcinoma: 5-year Results and Implication of Increased Low-Grade Rectal Complication on Initiation of an HDR-IC Fractionation Scheme". *Int. J. Radiat. Oncol. Biol. Phys.*, 1997, *38*, 391.

[10] Pötter R., Knocke T.H., Fer C., Baldass M., Reinthaller A., Kucera H.: " Definitive radiotherapy based on HDR brachytherapy with iridium 192 in uterine cervix carcinoma: report on the Vienna University Hospital findings (1993-1997) compared to the preceding period in the context of ICRU 38 recommendations". *Cancer Radiother.,* 2000, *4,* 159.

[11] Yamashita H., Nakagawa K., Tago M., Shiraishi K., Nakamura N., Ohtomo K.: "Treatment results and prognostic analysis of radical radiotherapy for locally advanced cancer of the uterine cervix". *Br. J. Radiol.,* 2005, *78,* 821.

[12] Pötter R., Dimopoulos J., Georg P., Lang S., Waldhäusl C., Wachter-Gerstner N. *et al.*: "Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer". *Radiother. Oncol.*, 2007, *83,* 148.

[13] Logsdon M.D., Eifel P.J.: "FIGO IIIB Squamous cell carcinoma of the cervix: an analysis of prognostic factors emphasizing the balance between external beam and intracavitary radiation therapy". *Int. J. Radiat. Oncol. Biol. Phys.*, 1999, *43*, 763.

[14] "LENT SOMA scales for all anatomic sites". *Int. J. Radiat. Oncol. Biol. Phys.,* 1995, *31*, 1049.

[15] Trotti A., Byhardt R., Stetz J., Gwede C., Corn B., Fu K. *et al.*: "Common toxicity criteria: Version 2.0 an improved reference for grading the acute effects of cancer treatment: Impact on radiotherapy". *Int. J. Radiat. Oncol. Biol. Phys.,* 2000, *47*, 13.

[16] Trotti A., Colevas A.D., Setser A., Rusch V., Jaques D., Budach V. *et al.*: "CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment". *Semin. Radiat. Oncol.,* 2003, *13,* 176.

[17] Hanlon A.L., Schultheiss T.E., Hunt M.A., Movsas B., Peder R.S., Hanks G.E.: "Chronic rectal bleeding after high-dose conformal treatment of prostate cancer warrants modification of existing morbidity scales". *Int. J. Radiat. Oncol. Biol. Phys.,* 1997, *38,* 59.

[18] Boersma L.J., van den Brink M., Bruce A.M., Shouman T., Gras L., Velde A. *et al.*: "Estimation of the incidence of late bladder and rectum complications after high-dose (70-78 GY) conformal radiotherapy for prostate cancer, using dose-volume histograms". *Int. J. Radiat. Oncol. Biol. Phys.*, 1998, *41*, 83.

[19] Trotti A., Bentzen S.M.: "The need for adverse effects reporting standards in Oncology clinical trials". *J. Clin. Oncol.,* 2004, *22*, 19.

[20] Bentzen S.M., Vaeth M., Pedersen D.E., Overgaard J.: "Why actuarial estimates should be used in reporting late normal-tissue effects of cancer treatment". *Int. J. Radiat. Oncol. Biol. Phys.*, 1995, *32,* 1531.

[21] Bentzen S.M., Dorr W., Anscher M.S., Denham J.W., Hauer-Jensen M., Marks L.B., Williams J.: "Normal tissue effects: Reporting and analysis". *Semin. Radiat. Oncol.*, 2003 *13*, 189.

[22] Bentzen S.M., Trotti A.: "Evaluation of early and late toxicities in chemoradiation trials". *J. Clin. Oncol.*, 2007, *25,* 4096.

[23] Dimopoulos J., Petrow P.: "Contouring of GTV, CTV and OAR. CT and MR Imaging, GYN GEC ESTRO Recommendations". *Radiother. Oncol.*, 2007, *83* (suppl. 1), 7.

[24] Viswanathan A.K., Dimopouos J., Kirisits C., Berger D., Pötter R.: "Computed tomography versus magnetic resonance imaging-based contouring in cervical cancer brachytherapy: resulsts of a prospektive trial and preliminary guidelines for standardized contours". *Int. J. Radiat. Oncol. Biol. Phys.,* 2007, *68,* 491.

[25] Haie-Meder C., Pötter R., van Limbergen E., Briot E., De Brabandere M., Dimopoulos J. *et al.*: "Recommendations from gynaecological (GYN) GEC-ESTRO working group: concepts and terms in 3D image-based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV". *Radiother. Oncol.*, 2005, *74*, 235.

[26] Pötter R., Haie-Meder C., van Limbergen E., Barillot I., De Brabandere M., Dimopoulos J. *et al.*: "Recommendations from gynaecological (GYN) GEC-ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology". *Radiother. Oncol.,* 2006, *78,* 67.

[27] Portelance L., Chao C., Grigsby P.W., Bennet H., Low D.: "Intensity-Modulated Radiation Therapy (IMRT) reduces small bowel, rectum, and bladder doses in patients with cervical cancer receiving pelvic and para-aortic irradiation". *Int. J. Radiat. Oncol. Biol. Phys.*, 2001, *51,* 261.

[28] Roeske J.C., Bonta D., Mell L.K., Lujan A.E., Mundt A.J.: "A dosimetric analysis of acute gastrointestinal toxicity in women receiving intensity-modulated whole-pelvic radiation therapy". *Radiother. Oncol.,* 2003, *69,* 201.

[29] Mundt A.J., Lujan A.E., Rotmensch J., Waggoner S.E., Yamada S.D., Fleming G. *et al.*: "Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies". *Int. J. Radiat. Oncol. Biol. Phys.,* 2002, *52,* 1330.

Address reprint requests to:
E. LORENZ, M.D.
Elvehavna medisinske senter
Beddingen 14
N 7014 Trondheim (Norway)
e-mail: elke.lorenz@stolav.no