Evaluation of morbidity after external radiotherapy and intracavitary brachytherapy in 771 patients with carcinoma of the uterine cervix or endometrium

D. Yalman, A. Arican, Z. Özsaran, Ö. K. Çelik, V. Yürüt, M. Esassolak, A. Haydaroglu

Ege University Faculty of Medicine Department of Radiation Oncology, Izmir (Turkey)

Summary

Purpose: The aim of the present study was to evaluate early and late radiation morbidity and to assess the factors influencing morbidity in patients with cervical or endometrial cancer treated by a combination of external radiotherapy (ERT) and intracavitary brachytherapy (IBRT).

Materials and methods: Early and late radiation morbidity were evaluated retrospectively using RTOG/EORTC criteria and Franco-Italian glossary in 771 patients treated between November 1992 and December 1999.

Results: Four hundred and seven patients (52.8%) had endometrial carcinoma and 364 (47.2%) had carcinoma of the cervix. One hundred and fifty-four patients with cervical carcinoma were inoperable. In patients with endometrial carcinoma total doses at the vagina, bladder and rectum were 60.36 Gy, 56.2 Gy and 55.6 Gy respectively. Biologically equivalent doses (BED) for the same points were 79.35, 68.63 and 67.37, respectively for early effects and 123.67, 97.65 and 94.85, respectively for late effects. One hundred and sixty-nine patients (41.5%) developed acute morbidity, grade I and II bladder morbidity being the most common type and 85 patients (20.9%) developed late morbidity, grade I and II vaginal morbidity being the most common type. No grade IV morbidity was recorded. Total doses at the vagina, bladder and rectum in operated cervix cancer patients were 60.51 Gy, 56.53 Gy and 55.67 Gy, respectively. BED for the same points were 79.77, 69.36 and 67.52, respectively for early effects and 124.74, 99.3 and 95.17, respectively for late effects. Eighty patients (38.1%) developed early morbidity. Grade I and II bladder morbidity was the most common type. Sixty-five patients (30.9%) developed late morbidity, vaginal morbidity being the most common type. Total doses at the vagina, bladder and rectum in inoperable patients were 70.92 Gy, 66.71 Gy and 62.38 Gy, respectively. BED for the same points were 97.43, 89.64 and 81.63, respectively for early effects and 159.3, 143.16 and 126.56, respectively for late effects. Sixty patients (39%) developed acute morbidity which was grade I or II bladder morbidity in 95%. Ninety-five patients (61.7%) developed late morbidity which was grade I-III vaginal morbidity in 94%.

Conclusion: Patients with cervical or endometrial cancer can be treated safely by a combination of ERT and IBRT. However the patients should be assessed before, during and after treatment and at every period of follow-up using a standard and well-defined system in order to define and predict the morbidity rate.

Key words: Morbidity; External radiotherapy; Intracavitary brachytherapy; Carcinoma of the uterine cervix; Endometrial carcinoma.

Introduction

Radiotherapy is a curative treatment modality for many patients with gynaecological cancer. Intracavitary brachytherapy (IBRT) in combination with external radiotherapy (ERT) has been widely used in the treatment of endometrial carcinoma and carcinoma of the uterine cervix. The aim of the treatment is to achieve maximum local control with minimal treatment-related complications. However radiotherapy is accompanied by specific acute and late complications involving different systems and organs in different degrees of frequency and severity. Careful registration of morbidity after cancer treatment is very important. Many studies reporting treatment results lack a description of morbidity. The reason for this could be the lack of a uniform and acceptable classification system for reporting morbidity although there are various proposals [1-5]. The aim of the present study was to perform a retrospective analysis of early and late radiation morbidity in patients with cervical or endometrial cancer treated by a combination of ERT and IBRT and to assess the factors influencing morbidity.

Presented at the Annual Meeting of the "Groupe European de Curiethérapie" - European Society for Therapeutic Radiology and Oncology, Stresa, Italy, June 7-9.

Revised manuscript accepted for publication August 7, 2001

Materials and Methods

From November 1992 to December 1999, 771 patients with carcinoma of the uterine cervix or endometrium were treated with a combination of ERT followed by IBRT at Ege University Faculty of Medicine, Department of Radiation Oncology. ERT was delivered by a 6-25 MV linear accelerator through AP/PA pelvic portals including the tumor and regional lymph nodes. The pelvic box technique was used in obese patients. Median total ERT dose was 54 Gy in operated patients and 59.4 Gy in inoperable patients (with parametrial boost after 54 Gy) delivered in 1.8 Gy daily fractions, 5 fractions per week. Midline shielding was performed at 50.4 Gy. One fraction of 9.25 Gy was given to a depth of 5-9 mm from the vaginal surface in operated patients with the ovoids of the Rotterdam applicator and two fractions of 8.5 Gy with weekly intervals were applied to point A in inoperable patients with the Rotterdam applicator via microSelectron-HDR remote afterloader Ir-192.

The records of the patients were evaluated retrospectively to assess early and late radiation morbidity. Early morbidity was defined as complications occurring within three months after radiotherapy and late morbidity as those complications occurring after more than three months. Only the side-effects for the rectum, bladder and vagina were assessed since these were the organs most at risk when ERT and IBRT were combined. The morbidity was recorded as mild, moderate or severe according to the patient's complaints, physical and gynecological examination and laboratory findings (urinalysis). After combining all the findings they were graded using RTOG/EORTC early and late radiation morbidity criteria [5]. They were scored at the highest degree of severity reached. The RTOG system does not include vaginal morbidity but many of the patients were suffering from vaginal morbidity (vaginal narrowing and/or shortening, dyspareunia) so the vaginal morbidity was graded according to the Franco-Italian glossary [1].

The statistical significance of differences between categorical variables was tested with the chi-square test. Values of p smaller than or equal to 0.05 were considered significant.

Results

Of the 771 patients 407 (52.8%) had endometrial and 364 (47.2%) had cervical carcinoma. Median age of the patients with endometrial carcinoma was 58. Most of the cases (65.9%) had FIGO Stage I disease and histologically most of them (78.6%) were adenocarcinoma. The characteristics of these patients are indicated in Table 1.

Median ERT dose for the patients with endometrial cancer was 54 Gy (biologically equivalent dose for early effects: BED_{10}= 63.72 and biologically equivalent dose for late effects: BED_3= 86.40) and median IBRT dose was 9.25 Gy (BED_{10}= 17.81, BED_3= 33.77). Median total doses (ERT+IBRT) at the vagina, bladder (b_0: bladder reference point according to ICRU recommendations) and rectum (r_0: rectal reference point according to ICRU recommendations) were 60.36 Gy, 56.2 Gy and 55.6 Gy, respectively (Table 2).

One hundred and sixty-nine patients (41.5%) developed different levels of acute radiation morbidity. In 11 (6.5%) cases more than one organ was involved. Acute bladder morbidity (mostly dysuria and increased frequency) was the most common early complication (Table 3). Eighty-five patients (20.9%) developed late radiation morbidity (Table 4). In eight (9.4%) cases more than one organ was involved. No grade IV early or late morbidity was recorded.

Of the 364 patients with cervix carcinoma 210 (57.7%) were operated on and 154 (42.3%) were inoperable. Median age of the patients was 49. Most of the cases (52.3%) had FIGO Stage II disease and histologically most of them (83.6%) were epidermoid carcinoma. The characteristics of these patients are indicated in Table 5.

Median ERT and median IBRT doses and median total doses (ERT+IBRT) at the vagina, bladder and rectum for the operated cervix cancer patients were similar with those of endometrial cancer patients due to our treatment protocol for operated patients (Table 6).

Table 1. — *Characteristics of patients with endometrial carcinoma.*

	No. of patients	%
Age		
Median 58 (Range: 29-81)		
Histologic type		
Adenocarcinoma	320	78.6
Clear cell	24	5.9
Adenosquamous ca.	13	3.2
Others	50	12.3
FIGO stage		
I	257	63.1
II	68	16.7
III	59	14.5
IV	6	1.5
Status unknown	17	4.2

Table 2. — *Median total doses and BED at reference points in patients with endometrial cancer.*

Reference points	Median total dose (Gy)	BED_{10}	BED_3
Tumor	59.65	77.38	118.41
Vagina	60.36	79.35	123.67
Bladder (b_0)	56.20	68.63	97.65
Rectum (r_0)	55.60	67.37	94.85

Table 3. — *Early radiation morbidity in patients with endometrial cancer.*

Organs at risk	Grade I	Grade II	Grade III	Total
Bladder	92 (22.6%)	42 (10.3%)	1 (0.25%)	135 (33.2%)
Rectum	25 (6.1%)	4 (1%)	1 (0.25%)	30 (7.3%)
Vagina	4 (1%)	–	–	4 (1%)
Total	121 (29.7%)	46 (11.3%)	2 (0.5%)	169 (41.5%)

Table 4. — *Late radiation morbidity in patients with endometrial cancer.*

Organs at risk	Grade I	Grade II	Grade III	Total
Bladder	5 (1.2%)	11 (2.7%)	1 (0.25%)	17 (4.2%)
Rectum	2 (0.5%)	8 (2%)	2 (0.5%)	12 (2.9%)
Vagina	24 (5.9%)	28 (6.8%)	4 (1%)	56 (13.8%)
Total	31 (7.6%)	47 (11.5%)	7 (1.7%)	85 (20.9%)

Table 5. — *Characteristics of patients with cervix carcinoma.*

	No. of patients	%
Age		
Median 49 (Range: 26-85)		
Operated patients	210	57.7
Inoperable patients	154	42.3
Histologic type		
Epidermoid carcinoma	301	82.7
Adenocarcinoma	47	12.9
Adenosquamous ca.	6	1.6
Others	10	2.7
FIGO stage		
I	130	35.7
II	182	50.0
III	32	8.8
IV	4	1.1
Status unknown	16	4.4

Eighty patients (38.1%) with operated cervix cancer developed acute radiation morbidity, with bladder complications being the most frequent (Table 7). No grade III or IV acute morbidity was recorded. In six patients (7.5%) more than one organ was involved. Sixty-five patients (30.9%) developed late radiation morbidity, with vaginal complications being the most frequent (Table 8). In three patients (4.6%) more than one organ was involved.

Median ERT dose for the patients with inoperable cervix cancer was 59.4 Gy (BED_{10}= 70.09, BED_3= 95.04) and median IBRT dose was 17 Gy (BED_{10}= 31.45, BED_3= 65.17). Median total doses (ERT+IBRT) at the vagina, bladder and rectum were 70.92 Gy, 66.71 Gy and 62.38 Gy, respectively (Table 9).

Sixty patients (38.9%) developed acute radiation morbidity, with bladder complications being the most frequent (Table 10). In two (3.3%) cases more than one organ was involved. No grade III or IV acute morbidity nor any vaginal morbidity was recorded.

Ninety-five patients (61.6%) developed late radiation morbidity, again with vaginal complications being the most common (Table 11). In four (4.2%) cases more than one organ was involved.

We analysed the possible factors which could influence morbidity such as age, prior surgery, stage, treatment-related parameters including total doses to the vagina, rectum and bladder and total midline dose. Age and stage failed to reveal any correlation with the development of acute or late morbidity. Late morbidity was more frequent in inoperable patients ($p < 0.001$). Total doses at the vagina, rectum and bladder did not reveal any correlation with either early or late morbidity of these organs. However total midline dose affected late morbidity in operated cases ($p = 0.005$). Late morbidity was frequent in patients with a total midline dose higher than the median value (59.65 Gy, BED_3= 118.41). In inoperable patients none of the above factors revealed any correlation with the development of early or late morbidity.

Table 6. — *Median total doses and BED at reference points in operated patients with cervix cancer.*

Reference points	Median total dose (Gy)	BED_{10}	BED_3
Tumor	59.65	77.38	118.41
Vagina	60.51	79.77	124.74
Bladder (b_0)	56.53	69.36	99.30
Rectum (r_0)	55.67	67.52	95.17

Table 7. — *Early radiation morbidity in operated patients with cervix carcinoma.*

Organs at risk	Grade I	Grade II	Total
Bladder	40 (19%)	26 (12.4%)	66 (31.4%)
Rectum	4 (1.9%)	5 (2.4%)	9 (4.3%)
Vagina	5 (2.4%)	–	5 (2.4%)
Total	49 (23.3%)	31 (14.8%)	80 (38.1%)

Table 8. — *Late radiation morbidity in operated patients with cervix carcinoma.*

Organs at risk	Grade I	Grade II	Grade III	Total
Bladder	5 (2.4%)	8 (3.8%)	2 (0.9%)	15 (7.1%)
Rectum	2 (0.9%)	4 (1.9%)	2 (0.9%)	8 (3.8%)
Vagina	19 (9%)	17 (8.1%)	6 (2.9%)	42 (20%)
Total	26 (12.4%)	29 (13.8%)	10 (4.7%)	65 (30.9%)

Table 9. — *Median total doses and BED at reference points in patients with inoperable cervix carcinoma.*

Reference points	Median total dose (Gy)	BED_{10}	BED_3
Tumor	67.40	90.92	145.81
Vagina	70.92	97.43	159.30
Bladder (b_0)	66.71	89.64	143.16
Rectum (r_0)	62.38	81.63	126.56

Table 10. — *Early radiation morbidity in patients with inoperable cervix carcinoma.*

Organs at risk	Grade I	Grade II	Total
Bladder	28 (18.2%)	29 (18.8%)	57 (37%)
Rectum	3 (1.9%)	–	3 (1.9%)
Vagina	–	–	–
Total	31 (20.1%)	29 (18.8%)	60 (38.9%)

Table 11. — *Late radiation morbidity in inoperable patients with cervix carcinoma.*

Organs at risk	Grade I	Grade II	Grade III	Total
Bladder	–	–	–	–
Rectum	2 (1.3%)	4 (2.6%)	–	6 (3.9%)
Vagina	23 (14.9%)	63 (40.9%)	3 (1.9%)	89 (57.7%)
Total	25 (16.2%)	67 (43.5%)	3 (1.9%)	95 (61.6%)

Discussion

Although the aim of radiotherapy is to achieve maximum local control with minimal treatment-related complications, specific acute and late complications involving different systems and organs in different degrees of frequency and severity can develop either during the early or late period after radiotherapy. Late morbidity has a great influence on the patient's quality of life. There are many factors such as total dose, irradiation technique, fractionation and daily dose, use of midline shielding, etc., which influence the likelihood of complications both for ERT and IBRT [6, 7]. According to some authors cumulative doses to organs at risk have shown a greater predictive value resulting in higher complication rates as total doses to the rectum, bladder or pelvic sidewall increase [4, 6-9].

In the present study most of the early complications were related to the bladder. There are various reports related to bladder injury following definitive radiotherapy especially for patients with carcinoma of the cervix. The overall rate of urinary sequelae is reported to be about 8-12%, while the rate of moderate/severe sequelae is about 2-6% [9-11]. Since the patients receive both ERT and IBRT the doses to the posterior/inferior walls of the

bladder are high. It is very difficult to determine the exact dose delivered to the bladder. The bladder reference point is most commonly taken at the posterior surface of the Foley balloon. We use the same reference point in IBRT applications. In a study by Kapp et al. it was shown that dose calculation on radiographs at the Foley balloon seriously underestimates maximum doses to the bladder [12]. This finding was confirmed by another study of the same author [13]. Although the median dose that the bladder had received seemed within tolerance limits in the present study, underestimation of the maximum dose due to the bladder reference point could be the reason for acute bladder complications. Montana et al reported a 7% urinary sequelae following a 60.01-65.00 Gy total bladder dose in radiotherapy for cervical cancer; this rate is 5% following 65.01-70.00 Gy and increases thereafter up to 10.8% following a total dose of greater than or equal to 80.00 Gy [14]. In a study by Pourquier et al the same rates following the same doses were 9.1%, 13.0% and 28.0%, respectively [11]. Our overall late bladder morbidity rate of 4.2% is low and no grade IV morbidity was observed.

Mild or moderate vaginal stenosis was the most common late sequelae of the treatment in our study. This could be correlated with the high single fraction doses of IBRT. Sorbe and Smeds reported a 15% late complication rate and a very high incidence of vaginal stenosis following postoperative high-dose-rate intravaginal irradiation [15]. This was attributed to the high dose per fraction of 6 to 9 Gy and the prescription at a depth of 10 mm from the surface of the cylinder resulting in very high vaginal mucosal, bladder and rectal doses. Concerning that our fractionation schedule of one brachytherapy insertion delivering a single dose of 9.25 Gy in operated patients and two fractions of 8.5 Gy in inoperable patients would result in significant complications we altered our treatment schedule employing two fractions of 6.5 Gy in operated patients and three fractions of 6 Gy in inoperable patients and we limited our total ERT dose to 50.4 Gy in operated patients. Also, apart from radiotherapy, several factors – age of the patient, previous hysterectomy or other surgical procedures and number of deliveries which is very high in Turkish women – could contribute to vaginal morbidity.

The incidence of severe proctitis following the treatment of cervical cancer is reported as less than 4% when the maximal rectal dose is less than 80 Gy, 7-8% for 80-95 Gy and 13% for greater than or equal to 95 Gy [16, 17]. Our early and late rectal complication rate was low because the rectal doses in our patients were tolerable; this could be due to the type of applicator we use (Rotterdam applicator) which includes a rectal retractor to remove the anterior rectal wall away from the ovoids.

Considering all of the complications, our grade III morbidity rate was low and no grade IV morbidity was observed. This may be due to the fact that a more specific detailed classification system was not used. Also the lack of differentiation between acute side-effects and those that have to be considered late and treatment-related makes a comparison very difficult.

In the present study of several possible factors which could influence morbidity – age, stage, prior surgery and treatment-related parameters – age and stage failed to reveal any correlation with the development of early and late morbidity. However late morbidity was more frequent in inoperable patients ($p < 0.005$) possibly due to the higher total dose and the IBRT technique used. Among the treatment-related parameters including total doses to the vagina, rectum and bladder and total midline dose, only total midline dose affected late morbidity in operated cases ($p = 0.005$). Late morbidity was frequent in patients with a total midline dose higher than the median value (59.65 Gy, BED_3= 118.41). Our study failed to show any correlation of maximum doses to the bladder and rectum with complications. It should be kept in mind that target organ threshold doses are not reliable predictors of risk of radiation sequelae because they fail to take into account the volume of the organ included in the high dose region. The critical dose is an estimate of the volume of tissue exposed to a high radiation dose.

Treatment-related complications are difficult to assess and report because no uniform and acceptable classification system is available. Also the retrospective evaluation of morbidity may be biased by the subjective interpretation of complications by the radiotherapist and the patient's clinical situation. Patients should be assessed carefully before treatment - to assess pretreatment morbidity factors including previous surgery, age, co-existing disease, obesity, stage, etc. to see if they were suffering from an already existing complication - and during treatment, after the completion of treatment and during every period of follow-up using a standard, well-defined system which is suitable to assess every critical organ included in a certain type of treatment. The findings could then be more reliable and could be predictive of the outcome of the treatment both for local control and morbidity, thus offering better tumor control and better quality of life. Estimations of late effects based on experience from complications due to different total doses or dose-fractionation schemes could play an important role in the evaluation of new radiotherapy schedules and treatment strategies.

References

[1] Chassagne D., Sismondi P., Horiot J. C. *et al.*: "A glossary for reporting complications of treatment in gynecological cancers". *Radiother. Oncol.*, 1993, *26*, 195.

[2] LENT/SOMA Tables. *Radiother. Oncol.*, 1995, *35*, 27.

[3] Pedersen D., Bentzen S. M., Overgaard 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.

[4] Sinistrero G., Sismondi P., Rumore A., Zola P.: "Analysis of complications of cervix carcinoma treated by radiotherapy using the Franco-Italian glossary". *Radiother. Oncol.*, 1993, *26*, 203.

[5] Perez C. A., Brady L. W.: "Overview". In: Principles and Practice of Radiation Oncology, 2nd Ed. (eds.) Perez C. A., Brady L. W. Philadelphia, J. B. Lippincott, 1992, 51.

[6] Lanciano R. M., Martz K., Montana G. M., Hanks G. H.: "Influence of age, prior abdominal surgery, fraction size and dose on complications after radiation therapy for squamous cell cancer of the uterine cervix". *Cancer*, 1992, *69*, 2124.

[7] Noyes W. R., Peters N. E., Thomadsen B. R. *et al.*: "Impact of optimized treatment planning for tandem and ring, and tandem and ovoids, using high dose rate brachytherapy for cervical cancer". *Int. J. Radiat. Oncol. Biol. Phys.*, 1995, *31*, 79.

[8] Ogino I., Kitamura T., Okamoto N. *et al.*: "Late rectal complication following high dose rate intracavitary brachytherapy in cancer of the cervix". *Int. J. Radiat. Oncol. Biol. Phys.*, 1995, *31*, 725.

[9] Perez C. A., Breaux S., Bedwinek J. M. *et al.*: "Radiation therapy alone in the treatment of carcinoma of the uterine cervix. II. Analysis of complications". *Cancer*, 1984, *54*, 235.

[10] Crook J. M., Esche B. A., Chaplain G., Isturiz J., Sentenac I., Horiot J. C.: "Dose-volume analysis and the prevention of radiation sequelae in cervical cancer". *Radiother. Oncol.*, 1987, *8*, 321.

[11] Pourquier H., Delard R., Archille E., Daly N. J., Horiot J. C., Keiling R. *et al.*: "A quantified approach to the analysis and prevention of urinary complications in radiotherapeutic treatment of cancer of the cervix". *Int. J. Radiat. Oncol. Biol. Phys.*, 1987, *13*, 1025.

[12] Kapp K., Stuecklschweiger G., Kapp D., Hackl A.: "Dosimetry of intracavitary placements for uterine and cervical carcinoma: results of orthogonal film, TLD and CT-assisted techniques". *Radiother. Oncol.*, 1992, *24*, 137.

[13] Kapp K. S., Stuecklschweiger G. F., Kapp D. S., Poschauko J., Hackl A.: "Carcinoma of the cervix: analysis of complications after primary external beam radiation and Ir-192 HDR brachytherapy". *Radiother. Oncol.*, 1997, *42*, 143.

[14] Montana G. S., Fowler W. C.: "Carcinoma of the cervix: Analysis of bladder and rectal radiation dose and complications". *Int. J. Radiat. Oncol. Biol. Phys.*, 1989, *16*, 95.

[15] Sorbe B. G., Smeds A. C.: "Postoperative vaginal irradiation with high-dose-rate afterloading technique in endometrial carcinoma Stage I". *Int. J. Radiat. Oncol. Biol. Phys.*, 1990, *18*, 305.

[16] Perez C. A., Fox S., Lockett M. A., Grigsby P. W., Camel H. M., Galakatos 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] Pourquier H., Bubois J. B., Delard R.: "Cancer of the uterine cervix: Dosimetric guidelines for prevention of late rectal and rectosigmoid complications as a result of radiotherapeutic treatment". *Int. J. Radiat. Oncol. Biol. Phys.*, 1982, *8*, 1887.

Address reprint requests to:
D. YALMAN, M.D.
Ege Üniversitesi Tıp Fakültesi
Radyasyon Onkolojisi A. D.
35100 Bornoval/İzmir (Turkey)