Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Incidence of radiation toxicity in cervical cancer and endometrial cancer patients treated with radiotherapy alone versus adjuvant radiotherapy

Andrzej Roszak[a,b,d], *Żaneta Wareńczak-Florczak*[a,*], *Krystyna Bratos*[a,e], *Piotr Milecki*[b,c,f]

[a] *Greater Poland Cancer Centre, Department of Gynaecological Radiotherapy and Oncology, Garbary Street 15, 61-866 Poznan, Poland*
[b] *Karol Marcinkowski University of Medical Sciences, Department of Electroradiology, Garbary Street 15, 61-866 Poznan, Poland*
[c] *Greater Poland Cancer Centre, Department of Radiation Oncology, Garbary Street 15, 61-866 Poznan, Poland*

ARTICLE INFO

Article history:
Received 12 October 2011
Received in revised form
14 April 2012
Accepted 13 July 2012

Keywords:
Gynaecological cancers
Radiotherapy
Toxicity

ABSTRACT

Aim: The study was made to evaluate early and late toxicity in a diversified group of patients receiving definitive or adjuvant radiotherapy in terms of clinical diagnosis and treatment methods.

Background: Radiotherapy is a standard way of treatment in cervical and endometrial cancer patients, both as definitive and adjuvant therapy. But every radiation treatment may be involved with toxicity.

Materials and methods: A detailed analysis was performed of 263 patients with gynaecological cancer treated with definitive (90 patients with cervical cancer received radiochemotherapy or radiotherapy exclusively) and adjuvant radiotherapy (38 with cervical and 135 with endometrial cancer).

Results: Acute reactions were found in 51.3% and late reactions were found in 14.8% of patients. It was stated that early ($p < 0.007$) and late ($p < 0.003$) post radiation reaction appear more frequently in women treated with definitive than adjuvant radiotherapy. The analysis of the whole group revealed higher rate of toxicity, both early and late, in the gastrointestinal tract than in the urinary system ($p < 0.004$). Comparing the subgroups, it was found that intestinal reactions occurred more frequently in the definitive radiotherapy group than in the adjuvant one.

The occurrence of side effects was associated with the prolongation of total irradiation time due to necessary interruptions of radiotherapy. The comparison of the subgroups showed that interruptions occurred more frequently in patients receiving definitive rather than adjuvant radiotherapy (17.7–2.9%).

* *Corresponding author*. Tel.: +48 618850589/604623753; fax: +48 618850534.
E-mail addresses: andrzej.roszak@wco.pl (A. Roszak), zflorczak@poczta.onet.pl (Żaneta Wareńczak-Florczak), krystyna.bratos@wco.pl (K. Bratos), piotr.milecki@wco.pl (P. Milecki).
[d] Tel.: +48 618850587; fax: +48 618850534.
[e] Tel.: +48 618850589; fax: +48 618850534.
[f] Tel.: +48 618850867.

http://dx.doi.org/10.1016/j.rpor.2012.07.005

Conclusions: Definitive radiotherapy compared with adjuvant treatment may by associated with higher percentage of side effects caused by dose of therapy and correlation with chemotherapy.

1. Background

Endometrial cancer is the fourth most frequent type of cancer affecting women in Poland, following breast, lung and colon cancers, while cervical cancer is right behind it.[1] Radiotherapy, alongside with surgery and chemotherapy, is an important part of the therapeutic process in women suffering from these cancers. Irradiation of the pelvis is the key component of a definitive or adjuvant treatment of cervical and endometrial cancer patients. The planning target volume (PTV), apart from the target itself (tumour or bed after excision of the tumour and the lymph nodes), comprises a number of healthy structures and organs, including the intestines and bladder. These organs, both during and after irradiation, are affected with early and late toxicity associated with destructive activity of ionising radiation. In many studies, authors have underlined that around 50% of patients irradiated to the pelvis exhibit radiation toxicity during radiotherapy.[2–5] It is associated with a treatment method (radical radiotherapy including in combination with chemotherapy or adjuvant radiotherapy) and radiation dose (combining teleradiotherapy and brachytherapy). Analysing radiation toxicity in relation to varied and ever changing treatment methods is as important as it is difficult.

2. Aim

The aim of this study is to analyse early and late radiation effects in a diversified group of patients receiving both definitive and adjuvant radiotherapy in terms of clinical diagnosis and treatment methods.

3. Materials and methods

3.1. *Patients and treatment*

The study covered 263 cervical cancer (CC) and endometrial cancer (EC) patients receiving definitive or adjuvant radiotherapy at the Radiotherapy and Gynecologic Oncology Department of the Greater Poland Cancer Centre. The recruitment process took 12 months, from May 2006. Due to different diagnosis (CC and EC) and different treatment methods (definitive or adjuvant radiotherapy), the patients were divided into two subgroups that were compared both internally and with each other.

The first subgroup consisted of 90 women with diagnosed FIGO stage IIB and IIIB cancer of the cervix treated with radical radiotherapy (radiotherapy exclusively or radiochemotherapy). All analysed patients received both external-beam radiation therapy (EBRT) and brachytherapy (BRT). Of them, 29 were managed with radiotherapy (RT) only, the other 61 were given radiochemotherapy (RCHT) – cisplatin at 40 mg/m^2 administered once a week over the radiotherapy period.

The RT patients had not been qualified for combined treatment (RCHT) not only because of their old age (they tended to be older than RCHT patients), but also due to concomitant diseases, such as kidney failure induced by advanced neoplasm.

External conformal radiotherapy was performed using four beams controlled by leaves of a multi-leaf collimator. Clinical target volume (CTV) comprised the tumour of the cervix along with the corpus uteri, vaginal wall and fornix, parametrium and lymph nodes of the pelvis. Fractionation dose was 1.8 Gy given 5 times a week. In the area of higher dose of LDR brachytherapy (BRT LDR), a central shield was used during teleradiotherapy assuming an ICRU-compliant dose of 85 Gy to point A. The correctness of teleradiotherapy was evaluated with portal images and in vivo dosimetry. In the case of brachytherapy, both physical and biological doses (EQD2) were measured.

An average EBRT dose in this group of patients was 48.2 Gy (range 12.6–54 Gy); an average BRT LDR dose was 44 Gy (20–60 Gy). In the group treated with HDR brachytherapy, patients received 28 Gy in 4 fractions and a total external beam dose of 45 Gy/T. For the IIIB stage patients, an external beam dose to the parametrium was increased to 50.4 Gy/T.

The other subgroup consisted of 173 patients receiving an adjuvant radiotherapy following surgery for FIGO stage IB-IIA cervical cancer (38 patients) and FIGO stage I-IIIA endometrial cancer (135 patients). Qualified to the adjuvant radiotherapy group were patients with poor prognostic factors from histopathological tests.

Conformal external-beam radiotherapy, as in the case of definitive radiotherapy, was delivered using four beams controlled by leaves of a multileaf collimator; 15 patients were treated with inter modulate radiation therapy (IMRT). The target volume included the lymph nodes of the pelvis. The fractionation dose was 1.8 Gy delivered 5 times a week. Total average dose to the planning target volume was 43.4 Gy/T ± 5 Gy.

All the patients received high dose rate (HDR) brachytherapy – 3 fractions of 6.0 Gy each, administered weekly. The dose was fixed at 0.5 cm from the applicator surface, its diameter adjusted to the anatomy of patient's vagina (2.0–4.0 cm).

3.2. *Methodology*

The patients were observed prospectively in the course of treatment (evaluations were made weekly) and at control examinations during a two-year follow-up. They were analysed for general health status, laboratory test results and radiation reactions from the intestines and urinary system. The analysis related to the course of radiotherapy, including

Table 1 – Analysis of radiotherapy interruption of more than 7 days in both subgroups.

Treatment method Number and % of patients	Cause of interruption	Location of toxicity (number and % of patients)
	Bladder	Intestines
Definitive radiotherapy 16 (17.7%)	3 (18.8%)	13 (81.2%)
Adjuvant radiotherapy 5 (2.9%)	0 (0%)	5 (100%)

interruptions in radiotherapy. The radiotherapy was evaluated based on medical documentation and irradiation sheets. Subject to investigation was both early and late toxicity (occurring later than 90 days after radiotherapy) observed during a two-year follow-up. In order to achieve the aim of the study, that is to evaluate radiation toxicity, the EORTC/RTOG scale was used. In further analysis, grade 1 and 2 reactions were collectively rated as mild, while grade 3 and 4 reactions were rated as severe.

The statistical analysis was carried out using the Chi-square, Mann–Whitney *U*, and Fisher's tests. The study employed FIGO classification applicable at that time, before the modification of 2009.

4. Results

4.1. *Analysis of the whole studied group and comparison of selected subgroups*

Early toxicity was found in 51.3% of all analysed patients. It occurred more often in the definitive radiotherapy group (27%), than in the adjuvant radiotherapy group (24.3%); the difference being statistically significant ($p < 0.007$).

Late toxicity occurred in 14.8% of patients, including 9.9% of those treated with definitive radiotherapy and 4.9% treated with adjuvant radiotherapy. Just like for early toxicity, the difference was statistically significant ($p < 0.006$).

The analysis of the whole studied group (263 patients) revealed higher rate of toxicity, both early and late, in the gastrointestinal tract than the urinary system ($p < 0.004$). Comparing the subgroups, it was found that intestinal reactions occurred more frequently in the definitive radiotherapy group than in the adjuvant radiotherapy group.

Analysing the subgroup of cervical cancer patients treated with definitive radiotherapy, it was found that patients given radiotherapy exclusively were statistically significantly older than those receiving radiochemotherapy. The mean age of patients treated with radiotherapy was 64.6 years ± 11.3 versus 51.6 years ± 8.5 for those treated with radiochemotherapy.

In the adjuvant radiotherapy group, patients with endometrial cancer were statistically significantly older than those with cervical cancer ($p < 0.002$). The mean age of patients with diagnosed cancer of the endometrial was 64.9 years ± 8.2 versus 54.0 years ± 8.7 for patients with cancer of the cervix.

The occurrence of side effects was associated with the prolongation of total irradiation time due to necessary interruptions of radiotherapy, including longer than seven days. This applied mostly to older patients in both subgroups (definitive and adjuvant radiotherapy). The comparison of the subgroups showed that interruptions occurred more frequently in patients receiving definitive radiotherapy than in those treated with adjuvant radiotherapy (17.7% and 2.9%, respectively) – see Table 1. These were mainly caused by intestinal toxicity.

Analysing radiotherapy interruptions of more than seven days, it was found that in the definitive radiotherapy subgroup the interruptions were correlated with a treatment method, occurring more often in patients treated with RT than in those treated with RCHT (10.0% and 7.7%, respectively). In the adjuvant radiotherapy subgroup, the incidence of radiation toxicity correlated with clinical diagnosis, with endometrial cancer patients showing more frequent therapy interruptions than cervical cancer patients (2.3% and 0.6%, respectively)

4.2. *Evaluation of early radiation toxicity*

The rate of early radiation toxicity was higher in the intestines than in the bladder (33.1% and 22.1%, respectively, for all patients).

Data regarding early radiation effects were presented independently for the intestines and the bladder broken down into four subgroups: definitive radiotherapy (cervical patients treated with RT or RCHT) and adjuvant radiotherapy (patients with CC and EC).

Shown below is the analysis of early toxicity in the gastrointestinal tract. Results are presented in Table 2.

The highest rate of intestinal toxicity was recorded in cervical cancer patients receiving definitive radiotherapy, of which 65.5% were treated with RT and 37.7% with RCHT. Of note is a high percentage of patients with severe complications (grades 3 and 4). These were also patients managed with definitive radiotherapy (24.1% in the RT group and 26.2% in the RCHT group). Intestinal reactions occurred much less often after adjuvant therapy.

Analogous analysis was made for early toxicity in the bladder. Results are shown in Table 3.

Notably, early radiation toxicity in the bladder was less frequent than that in the intestines, its incidence being the highest (36.9%) in patients with cervical cancer (CC) receiving adjuvant radiotherapy after surgery. In the same subgroup, aside from cervical cancer patients treated with RT, the analysis showed a relatively high proportions of severe effects, i.e. 8.0% and 10.4%, respectively.

Table 2 – Early radiation intestinal toxicity in the intestines in patients receiving definitive (RCHT and RT) and adjuvant (CC and EC) radiotherapy – EORTC scale.

Treatment method/clinical diagnosis Number of patients (toxicity rate)	Toxicity grade (number and % of patients)		
	Grade 0	Grades 1 and 2	Grades 3 and 4
RCHT 61 (37.7%)	38 (62.3%)	7 (11.5%)	16 (26.2%)
RT 29 (65.5%)	10 (34.5%)	12 (41.4%)	7 (24.1%)
CC 38 (23.7%)	29 (76.3%)	6 (15.8%)	3 (7.9%)
EC 135 (26.7%)	99 (73.3%)	24 (17.8%)	12 (8.9%)

Table 3 – Early radiation toxicity from the bladder in patients receiving definitive (RCHT and RT) and adjuvant (CC and CE) radiotherapy – EORTC scale.

Treatment method/clinical diagnosis Number of patients (toxicity rate)	Toxicity grade (number and % of patients)		
	Grade 0	Grades 1 and 2	Grades 3 and 4
RCHT 61 (21.3%)	48 (78.7%)	9 (14.7%)	4 (6.6%)
RT 29 (20.8%)	23 (79.2%)	3 (10.4%)	3 (10.4%)
CC 135 (36.9%)	24 (63.1%)	11 (28.9%)	3 (8.0%)
EC 135 (18.5%)	110 (81.5%)	23 (17.0%)	2 (1.5%)

Table 4 – Late intestinal toxicity in patients receiving definitive (RCHT and RT) and adjuvant radiotherapy (CC and EC), EORTC scale.

Treatment method/clinical diagnosis Number of patients (toxicity rate)	Toxicity grade (number and % of patients)		
	Grade 0	Grades 1 and 2	Grades 3 and 4
RCHT 61 (21.3%)	48 (78.7%)	11 (18%)	2 (3.3%)
RT 29 (27.6%)	21 (72.4%)	7 (24.2%)	1 (3.4%)
CC 38 (10.5%)	34 (89.5%)	4 (10.5%)	0 (0.0%)
EC 135 (7.4%)	125 (92.6%)	10 (7.4%)	0 (0.0%)

Table 5 – Late radiation toxicity in the bladder in patients receiving definitive (RCHT and RT) and adjuvant radiotherapy (CC and EC), EORTC scale.

Treatment method/clinical diagnosis Number of patients (toxicity rate)	Toxicity grade (number and % of patients)		
	Grade 0	Grades 1 and 2	Grades 3 and 4
6.5% juice	57 (93.5%)	4 (6.5%)	0 (0.0%)
RT (3.4%)	26 (96.6%)	1 (3.4%)	0 (0.0%)
CC (2.6%)	37 (97.4%)	1 (2.6%)	0 (0.0%)
EC (1.5%)	133 (98.5%)	2 (1.5%)	0 (0.0%)

4.3. *Evaluation of late radiation toxicity*

Analysis results for late toxicity, as in the case of early toxicity, indicate higher incidence in the intestines than in the bladder (13.3% and 3.0%, respectively).

The results, as those for early toxicity, were presented separately for the intestines and the bladder and broken down into four subgroups: stand-alone radiotherapy (cervical patients treated with RT or RCHT) and adjuvant radiotherapy (patients with CC and EC).

Analysis results for late intestinal toxicity are shown in Table 4.

Of note is a low proportion of patients with severe late reactions. These were cervical cancer patients treated with radical irradiation (3.3% RCHT, 3.4% RT). No severe reactions were found in patients who had underwent adjuvant radiotherapy.

Below is the analysis of late toxicity in the bladder (Table 5).

Late radiation toxicity, in low grade only (1 and 2), occurred in several percent of patients.

5. Conclusion and discussion

5.1. *Conclusion*

1. Definitive radiotherapy, as compared to adjuvant radiotherapy, is associated with significantly higher incidence of early (27% and 24.3%, respectively) and late (9.9% and 4.8%, respectively) toxicity.
2. The whole studied group revealed a statistically significantly higher rate of radiation toxicity, both early and late, in the gastrointestinal tract as compared with the bladder (61% and 39%) – ($p < 0.004$).

3. Radiotherapy alone (both RT and RCHT) more often than adjuvant radiotherapy related to early and late radiation toxicity, including severe (grades 3 and 4) and intestinal complications ($p < 0.008$).
4. Early toxicity of the bladder was most prevalent in cervical cancer patients who had been treated with surgery.
5. Interruptions in radiotherapy of more than 7 days, caused by the occurrence of adverse radiation effects, were more often found in patients treated with radiotherapy alone (17.7%) than adjuvant radiotherapy (2.9%). This led to the prolongation of total treatment time in those patients.

5.2. *Discussion*

The aim of this study was to analyse the incidence of radiation side effects in cervical and endometrial cancer patients treated with various radiotherapy methods, including in combination with surgery (adjuvant radiotherapy) and chemotherapy (radiochemotherapy).

Early radiation toxicity (during and within 3 months after irradiation) occurred in 51.3% of all the analysed patients versus 14.8% of late toxicity. Similar results for comparable cervical and endometrial cancer groups have been reported in many publications analysing definitive and adjuvant radiotherapy.[2–7,33,36]

The analysis of patients managed in the Greater Poland Cancer Centre showed that a statistically higher percentage of patients who had developed both early and late radiation toxicity had received a stand-alone rather than adjuvant radiotherapy ($p < 0.007$ and $p < 0.006$). This should be associated with a higher physical and biological dose delivered to those patients' organs at risk. A higher dose to critical organs in this group of patients resulted from a higher dose to the parametrium in definitive external-beam radiation (by 5.4 Gy), as compared to patients treated with adjuvant radiotherapy, and from its being combined with LDR or HDR brachytherapy where doses were higher than in postoperative brachytherapy. The relationship between high dose and the risk of radiation toxicity during radiotherapy has been pointed out by such authors as Perez et al.,[8] Montana et al.,[9] Kootmeier[10] and Roszak et al.[35] All of them have observed complications increasing with higher radiation doses.

The whole studied group of 263 patients, regardless of radiotherapy method used, revealed a statistically significantly higher rate of radiation toxicity, both early and rate, in the gastrointestinal tract than in the bladder ($p < 0.004$). This should be accounted for by a lower tolerance dose of the intestines,[37] as compared to the bladder, a large volume of intestines covered by high dose irradiation, and patients' difficulties in maintaining their indicated nutrition regime. These factors were also highlighted in the study by Morris et al. analysing the occurrence of radiation toxicity in patients receiving radiation to the pelvic field.[11] Gastrointestinal toxicity was also the main reason for interruptions in radiotherapy in patients undergoing both radical and adjuvant treatment.

Age is another factor that may have affected treatment tolerance. The analysis made in this study showed statistically significant age differences between the two subgroups. Older patients had higher rate of complications. These results are consistent with those reported by Lanciano et al.,[12,13] where patients of 40 years and older where proved to develop higher toxicity.

In the definitive radiation therapy group, patients receiving radiotherapy only were statistically significantly older ($p < 0.01$) and it was them who showed more complications, whether early or late. In the adjuvant radiation group, endometrial cancer patients were statistically significantly older than cervical cancer patients ($p < 0.002$). The former were more frequently observed to develop concomitant diseases, such as hypertension, diabetes, asthma and obesity. The additional diseases and older age caused reactions occurring in these patients, even though less frequent during radiotherapy, to be more often of the type requiring radiotherapy to be interrupted for more than 7 days.

Analysing tolerance-related treatment interruptions, it was found that interruptions lasting more than 7 days occurred more often in patients treated with radiotherapy only than in those treated with adjuvant radiotherapy (17.7% and 2.9%, respectively). The interruptions led to the prolongation of total treatment time.

The toxicity analysis of both subgroups showed that out of all cervical patients treated with definitive radiotherapy, those receiving radiotherapy only had higher rate of complications, both early and late, as compared with patients receiving radiochemotherapy. These results differ from published reports. The NCIC study[14] found no difference in the occurrence of early and late radiation toxicity in two patients groups: those receiving radiochemotherapy and radiotherapy alone. Other authors, however, indicate an adverse effects of concurrent chemotherapy.[11] Results of our analysis may be related to our patients' high clinical stage of the disease; concurrence of renal failures and other diseases; as well as old age disqualifying them from radiochemotherapy.

It should be stressed that, despite higher gastrointestinal toxicity in the group treated with RT alone, severe complications occurred more frequently in patients receiving combined radiotherapy and chemotherapy, which may be related to the joint, synergistic activity of both modalities. The combination of two toxic factors leads to the increase in the rate of adverse reactions. This correlation has also been indicated by the authors of RTOG 90-01.[5] This effect, on one hand favourable in combating neoplastic cells, turns undesirable for healthy cells, such as those in the intestines, leading to increased incidence of acute toxicity in this organ.[7]

The group receiving adjuvant radiotherapy was also observed to show a high rate of grade 3 intestinal toxicity (no grade 4 reactions were recorded) both in cervical cancer patients (7.9%) and endometrial cancer patients (8.9%). Severe reactions during radiotherapy in the range of 3–5% have been observed by many authors.[15–22] It seems that the rate of grade 3 toxicity obtained in this study may have also been related to the application of the EORTC/RTOG scale. According to this scale, gastrointestinal toxicity is classified as grade 3 whenever parenteral hydration is required. Many patients, especially older ones, were given intravenous hydration, often longer than 24 h, for persisting diarrhoea.

The analysis of the rate of early toxicity in the bladder showed no significant differences in the incidence of complications between RT and RCHT patients. Similar results were

reported by NCIC,[14] RTOG 90-01[11] and Green's metaanalysis.[23] However, we observed more late reactions in patients receiving radiochemotherapy than radiotherapy alone. This may have been related to the use of cisplatin affecting the urinary system.

Of note, however, is early bladder radiation toxicity found in high percentage of postoperative cervical cancer patients. This in turn may have been associated with a larger scope of surgery as compared to endometrial cancer patients. Radiation toxicity may have also been intensified by surgery side effects, such as bladder dysfunction or infections in the lower part of the urinary system.[6,24–26,12,27,34]

A note should be taken that total radiation doses in patients treated with adjuvant radiotherapy were lower than in patients treated with radiotherapy alone. But the size of dose is only one of the factors determining the occurrence of radiation toxicity, aside from those commonly recognised, such as age, metabolic diseases, chronic gastrointestinal or urinary. The combination of external-beam radiotherapy and intravaginal brachytherapy increases the rate of both early and late radiation effects.[25,28–32]

Conflict of interest

None declared.

Financial disclosure

None declared.

REFERENCES

1. Dyzman-Sroka A, Myślińska W, Harska A, et al. *Cancer in the Greater Poland province in 2008*; 2010. p. 7.
2. Serkies K, Kobierska A, Konopa K, Sawicki T, Jassem J. The feasibility study on continuous 7-day-a-week external beam irradiation in locally advanced cervical cancer: a report on acute toxicity. *Radiother Oncol* 2001;**61**:197–202.
3. Weiss E, Hirnle P, Arnold-Bofinger H, Hess CF, Bamberg M. Therapeutic outcome and relation of acute and late side effects in the adjuvant radiotherapy of endometrial carcinoma stage I and II. *Radiother Oncol* 1999;**53**:37–44.
4. Wareńczak-Florczak Z, Roszak A, Bajon T. Ocena odczynów popromiennych wczesnych i późnych u chorych na zaawansowanego raka szyjki macicy poddanych radioterapii. *Wsp Onkol* 2009;**13**(6):330–3.
5. Wareńczak-Florczak Z, Roszak A, Włodarczyk H, et al. Ocena odczynów popromiennych wczesnych i późnych w radioterapii uzupełniającej u chorych na raka endometrium i raka szyjki macicy. *Contemp Oncol* 2011;**15**(1):15–9.
6. Jereczek-Fossa B, Bodzio A, Jassem J. Factors determining acute normal tissue reactions during postoperative radiotherapy in endometrial cancer: analysis of 317 consecutive cases. *Radiother Oncol* 2003;**68**:33–9.
7. Kirwan JM, Symonds P, Green JA, et al. A systematic review of acute and late toxicity of concomitant chemioradiation for cervical cancer. *Radiother Oncol* 2003;**68**:217–26.
8. Perez CA, Breaux S, Madoc-Jones H, et al. Radiotherapy alone in treatment of carcinoma of the cervix: analysis of tumor reccurence. *Cancer* 1983;**51**:1393–402.
9. Montana GS, Fowler WC, Varis MA, et al. Carcinoma of the cervix, stage III, results of radiation therapy. *Cancer* 1986;**57**:148–54.
10. Kootmeier HL. Complications fallowing radiation therapy in carcinoma on the cervix and their treatment. *Am J Obstet Gynecol* 1964;**88**:854–66.
11. Morris M, Eifel PJ, Grigsby PW, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical. *N Engl J Med* 1999;**340**:1137–43.
12. Lanciano RM, Martz K, Montana GS, et al. Influence of age, prior abdominal surgery, fraction size and dose on complication after radiation therapy for squamous cell cancer of the uterine cervix. *Cancer* 1992;**69**:2124–30.
13. Lanciano RM, Won M, Coia LR, et al. Pretreatment and treatment factors associated with improve outcome in squamous cell carcionoma of the uterin cervix: a final report of the 1973 and 1978 patterns of care studies. *Int J Radiat Oncol Biol Phys* 1991;**20**:667–76.
14. Pearcey RG, Mahamed IG, Hanson J. Treatment of high-risk cervical cancer. *N Engl J Med* 1999;**341**:695–6.
15. Stewart KD, Martinez AA, Weiner S, et al. Ten-year outcome including patterns of failure and toxicity for adjuvant whole adominopelvic irradiation in high-risk and poor histologic feature patients with endometrial carcinoma. *Int J Radiat Oncol Biol Phys* 2002;**54**:527–35.
16. Jareczek-Fossa B, Badzio A, Jassem J. Time without symptoms and toxicity (TWIST) analysis of adjuvant radiation therapy for endometrial cancer. *Radiother Oncol* 2004;**72**:175–81.
17. Algan O, Tabesh T, Hanlon WM, et al. Improved outcome in patients treated with postoperative radiation therapy for pathologic stage I/II endometrial cancer. *Int J Radiat Oncol Biol Phys* 1996;**35**:925–33.
18. Carey MS, O'Connell GJ, Johannson CR, et al. Good outcome associated with a standardized treatment protocol using selective postoperative radiation in patients with clinical stage I Aden carcinoma of the endometrium. *Gynecol Oncol* 1995;**57**:138–44.
19. Greven KM, Corn BW, Case D, et al. Which prognostic factors influence the outcome of patients with surgically stage endometrial cancer treated with adjuvant radiation? *Int J Radiat Oncol Biol Phys* 1997;**39**:413–8.
20. Kucera H, Vavra N, Weghaupt K. Benefit of external irradiation in pathologic stage I endometrial carcinoma: a prospective clinical trial of 605 patients who received postoperative vaginal irradiation and additional pelvic irradiation in the presence of unfavorable prognostic factors. *Gynecol Oncol* 1990;**38**:99–104.
21. Morrow CP, Bundy BN, Kurman RJ, et al. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group Study. *Gynecol Oncol* 1991;**40**:55–65.
22. Fugazzi J, Han I, Lo S, et al. Post-operative external beam radiotherapy and vaginal cuff brachytherapy boost for endometrial cancer: survival rates, site of failure and prognostic factors for recurrence. *Radiother Oncol* 2004:23.
23. Green JA, Gusberg SB, Guttman R, et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of uterin cervix; a systemic review and metaanalysis. *Lancet* 2001;**358**:781–6.
24. Jereczek-Fossa B, Jassem J, Badzio A. Relationship between acute and late normal tissue injury after postoperative radiotherapy in endometria cancer. *Int J Radiat Oncol Biol Phys* 2002;**52**:476–82.
25. Jereczek-Fossa B, Jassem J, Nowak R, et al. Late complications after postoperative radiotherapy in endometria cancer: analysis of 317 consecutive cases with application of linear-quadratic model. *Int J Radiat Oncol Biol Phys* 1998;**41**:329–38.

26. Mallett V, Bump R. The epidemiology of female pelvic floor dysfunction. *Curr Opin Obstet Gynecol* 1994;**6**:309–12.
27. Vervest HAM, Barents JW, Haspels AA, et al. Radical hysterectomy and function of lower urinary tract. *Acta Obstet Gynecol Scand* 1989;**68**:331–40.
28. Jereczek-Fossa B, Jassem J, Badzio A. Surgery followed by radiotherapy in endometria cancer: analysis of survival and patterns of failure. *Int J Gynecol Cancer* 1999;**9**:285–94.
29. Mayr NA, Wen B, Benda JA, et al. Postoperative radiation therapy in clinical stage I endometria cancer: corpus, cervical and lower uterine segment involvement – patterns of failure. *Radiology* 1995;**196**:323–8.
30. Randal ME, Wilder J, Greven K, et al. Role of intracavitary cuff boost after adjuvant external irradiation in early endometrial carcinoma. *Int J Radiat Oncol Biol Phys* 1990;**19**:49–54.
31. Stokes S, Bedwinek J, Breaux S, et al. Treatment of stage I adenocarcinoma of the endometrium by hysterectomy and irradiation: analysis of complications. *Obstet Gynecol* 1985;**65**:86–92.
32. Wolfson AH, Sighert SE, Markoe AM, et al. The prognostic significance of surgical staging for carcinoma of the endometrium. *Gynecol Oncol* 1992;**45**:142–6.
33. SerkiesF K., Krasińska L, Sawicki T, Jassem J. Concurrent weekly cisplatin and radiotherapy in cervical cancer patients: a report of acute toxicity. *Rep Pract Oncol Radiother* 2002;**7**(1):11–4.
34. Cybulski Z, Roszak A, Talaga Z, Grabiec A, Kaźmierska J. Urinary tract infections in patients with malignant neoplasms of the genitourinary system. *Rep Pract Oncol Radiother* 2005;**10**(1):23–6.
35. Roszak A, Skrobała A, Włodarczyk H, Malicki J. Wpływ teleradioterapii konformalnej na obniżenie dawek w narządach zdrowych u chorych z zaawansowanym rakiem szyjki macicy. *Rep Pract Oncol Radiother* 2004;**9**(S2):256.
36. Wieczorek A, Kędzierawski P, Smok-Kalwat J, Banatkiewicz P. Assessment of Elary toxicity of concomitant radiochemotherapy in the treatment of locally advanced cervical cancer. *Rep Pract Oncol Radiother* 2001;**6**(1):60.
37. Miquel Macià G, Calduch A, Casanovas Lopez E. Radiobiology of the acute radiation syndrome. *Rep Pract Oncol Radiother* 2011;**16**:123–30.