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ORIGINAL ARTICLE

Whole abdominal irradiation in endometrial cancer - A single institution study

L. Gocheva[1], B. Slavchev[2]

[1]Department of Radiotherapy, University Hospital "Queen Giovanna-ISUL", Sofia; [2]Department of Gynecologic Surgery, University Hospital "Maichin Dom", Sofia, Bulgaria

Summary

Purpose: *To examine the use of whole abdominal irradiation (WAI) open field technique in patients with stage III endometrial cancer (EC).*

Methods: *Between 1993 and 2007, 26 patients (age 39-70 years, median 58) with stage III EC (IIIA 15, IIIB 2, IIIC 8) were treated with WAI after primary surgery. Five (21%) patients had grade 1 disease, 18 (67%) grade 2 and 3 (12%) grade 3. In 2 (8%) patients a second laparotomy was carried out before the radiotherapy (RT) referral. Ascites and positive peritoneal cytology was present in 3 (15%) and 4 (20%) patients, respectively. After surgery, residua < 2 cm in the upper abdomen were left in 2 patients. WAI was delivered using Co 60 anterior-posterior photon fields to encompass the peritoneal cavity. In 84% of the patients WAI consisted of 30 Gy, delivered mainly in daily fractions of 1.5 Gy (81%), 5 fractions per week. For the remaining patients the dose was 25 Gy (8%) and 20 Gy (8%), respectively. After abdominal RT, 85% of the patients were given a pelvic boost to reach 45 - 50 Gy with 1.8 Gy/fraction/day, using a Co 60 unit. In 5 (19%) patients boost to 45-50 Gy with 1.8 Gy/fraction/day to other risk sites was also given. Two (8%) of 26 patients received 2 cycles of platinum-based chemotherapy. The mean follow-up time was 13.41 years.*

Results: *The treatment time ranged from 14-74 days, median 48. The overall survival (OS) rate was 93% at 5, 10 and 14 years. Ten (38.5%) patients received their treatment with no interruption, and in 16 (61.5%) patients RT was transiently interrupted because of acute gastrointestinal and hematological toxicity. Neither grade 4 acute complications nor mortality while receiving treatment were observed. Late side effects (grade 2 gastrointestinal complications) developed in 1 (5%) patient. During the observation period a second primary malignancy was recorded in 1 patient.*

Conclusion: *WAI achieves a quite favorable 5- and 14-year survival rate with an acceptable risk of acute and late side effects in properly selected patients with stage III EC. WAI as a sole or a part of combined treatment warrants further investigation in patients with high-risk EC.*

Key words: endometrial cancer, radiotherapy, whole abdominal irradiation

Introduction

EC, as a common, invasive gynecologic malignancy that kills thousands of women throughout the world each year, represents a life-threatening disease and its treatment is related to numerous challenges. In Bulgaria it has an annual mortality rate of 2.1/100 000 women [1].

The use of RT in patients with EC may have the form of preoperative irradiation, irradiation alone or postoperative irradiation. Specific RT modalities have changed significantly over time and depend on many factors, including technical aspects of the RT used and local geographic practice patterns.

It is well known that during the last decades, with the exception of ovarian tumors, WAI as a large field technique and as a systemic therapy in oncology, alternative to chemotherapy (CT), has found application in a number of other oncological diseases susceptible to development and dissemination in the abdomen. Among these the first place belongs to the endometrial and cervical cancer, as well as the primary tubal carcinoma [2-6].

As early as in the 1980s, a subset of patients with

Correspondence to: Lilia Gocheva, MD. Dimitar Nestorov 120 A, app.22, Sofia 1612, Bulgaria. Tel: +359 2 9432376, Fax: +359 2 9712600, E-mail: lgocheva2001@yahoo.co.uk

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EC was identified as being at high-risk. This included patients with high-grade lymphovascular invasion, clear cell and papillary serous histologic types or with positive adnexa and positive peritoneal cytologic findings, who were at high risk of failing in the paraaortic nodes and/or the upper abdomen for whom extended field or WAI have been advocated.

During the last decades a number of clinical studies investigated the therapeutic potential of WAI as an adjuvant treatment in high-risk EC patients. As early as in 1985, Potish et al. proved its therapeutic possibilities reaching 71% 5-year OS [7]. The prognostic importance of some of the above mentioned factors is also an object of intensive investigation, for example the depth of invasion, the existence of involved adnexa or positive peritoneal cytology as well as involved lymphatic chains [8-10].

The aim of the present single-institution study was to summarise the results of WAI open field technique used in patients with FIGO stage III EC during the years 1993-2007.

Table 1. Disease characteristics (n=26)

Characteristic	*Number of patients*	*%*
Stage		
III [IIIA, IIIB, IIIC]	26	100
Grade		
1	5	21
2	18	67
3	3	12
Histopathology		
Adenocarcinoma	18	69
Other	8	31
Second look laparotomy		
Yes	2	8
No	24	92
Ascites		
Yes	3	11
No	23	89
Peritoneal cytology		
Positive	4	15
Negative	8	31
Inconclusive	14	54
Chemotherapy		
Yes	2	8
No	24	92

Methods

Between 1993 and 2007, 26 FIGO stage III EC patients were treated with primary surgery and postoperative RT in the form of WAI open field technique at the Medical University of Sofia. Data of the patients were obtained from tumor registry, operative notes, pathology, RT chart reviews, and CT flow sheets. Characteristics of the patients based on the surgicopathologic findings and the distribution of potential prognostic factors are shown in Table 1.

The age distribution ranged from 39 to 70 years (median 58). Histologically adenocarcinomas predominated (n=18 / 69%). Five (21%) patients had grade 1 tumors, 18 (67%) grade 2, and 3 (12%) grade 3. In 2 (8%) patients a second look laparotomy was carried out before the RT referral, which revealed macroscopic residual disease < 2 cm was left after surgery, the localization of the residual disease being in the upper abdomen in both cases.

In first laparotomy ascites was present in 3 (11.5%) patients and in 46% of the patients peritoneal washings were positive in 4 (15%) of them.

CA-125, chest X-ray and computed tomography scan of the abdomen and pelvis were obtained pre- and postoperatively as a baseline for future comparison.

The applied routine surgical interventions in all of the patients consisted of total abdominal hysterectomy with bilateral salpingo-oophorectomy. In a part of the patients additional surgical procedures were carried out, including omentectomy, selective pelvic and paraaortic lymph node sampling, cytologic examination of ascites or peritoneal washings, thorough inspection of the abdomen and pelvis, and targeted biopsies of suspected metastases.

After surgery, patients were discussed at the multidisciplinary gynecologic oncology tumor board. Two (8%) patients received 2 cycles of platinum-based CT. Because of the nature of the study, CT was not given according to a program or protocol but according to the physician's preferences.

The RT technique, with clinical target volume (CTV) encompassing the entire peritoneal cavity, was as follows: parallel opposed anterior-posterior fields, extended source-surface distance (SSD), whole abdominal Co 60 photon fields delivered in daily fractions of 1.0-1.5 Gy (with most frequent application of 1.5 Gy / 81%), 5 fractions per week. The field borders extended from 1.5 cm above the diaphragms in quiet expiration, to 1 cm below the inferior aspect of the obturator foramen. Laterally the fields extended beyond the peritoneal reflection. Anterior/posterior kidney and hepatic shields were introduced at 16-20 Gy to maintain the total kidney and hepatic dose at less than 20 Gy. In 84% of the patients, the dose delivered was 30 Gy to the whole abdomen, and for the remaining the dose was 25 Gy (8%) and 20 Gy (8%), respectively. In 22 (85%) patients subjected to WAI open field technique, the pelvis was then given an additional dose, using most frequently 1.8 Gy/fraction (58%)

to reach a total pelvic dose of 45-50 Gy. Except in the pelvis, in 5 (19%) patients a boost was delivered to risk sites, also varying between 45 and 50 Gy. In most of the cases these were paraaortic lymphatic chains.

All patients were analyzed with regard to acute and late toxicity. Acute toxicity was recorded according to the common toxicity criteria (CTC) [11] and late toxicity was classified according to the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) guidelines [12]. Patients were evaluated for general tolerance and side effects weekly during RT. Antiemetic, antidiarrheal or other symptomatic medications were prescribed as required. Complete blood counts were obtained at least 2 times weekly, and daily if necessary. RT was temporarily withheld if the absolute neutrophil count was $<1 \times 10^9$/L or the platelet count $<50 \times 10^9$/L.

Statistical methods

Demographics and disease characteristics were summarized using descriptive statistics. OS, measured from the date of entry into the treatment protocol until death of any cause, was estimated according to the Kaplan-Meier method [13].

Results

The mean follow-up time was 13.41 years (range 0.29-14.15). The treatment time ranged from 14-74 days (median 48). The estimated 5-, 10-, and 14-years OS rate was 93% (Figure 1).

During the whole period of clinical observation (more than 50% of the patients survived 13 years) only one patient died at the third year. The rest of the patients are alive and with no evidence of disease.

Unfortunately, it was not possible to analyse the OS according to individual prognostic factors known in the relevant literature due to the small number of the observed cases. The fact that only one of all the 26 cases had a lethal outcome represented an additional restriction.

All patients were analyzed with regard to the most frequently observed and discussed acute and late gastrointestinal and hematological toxicity. Ten (38.5%) patients received their treatment with no interruption, and in 16 (61.5%) patients RT was temporarily interrupted because of acute toxicity. Treatment interruptions were for a median of 11 days (range 4-31). Reasons for interrupting treatment were gastrointestinal toxicity in 3 (19%) patients, hematological toxicity in 10 (62%) and other reasons (allergic dermatitis, hernia and lower limb phlebothrombosis) in 3 (19%). Most patients experienced grade 1 or 2 nausea or diarrhea or both during WAI. Control of the clinical symptoms was realized with antiemetic and antidiarrheal drugs. In 5 (56%) patients interruption was due to neutropenia (grade 1-3), in 3 (33%) to thrombocytopenia (grade 2-3) and in 1 (11%) to anemia (grade 1). Neither grade 4 acute complications nor mortality while receiving treatment were observed. Patients were carefully monitored during RT, and there were no serious consequences such as sepsis or hemorrhage. None of the patients required blood transfusion during treatment. All of these toxicities resolved upon cessation of treatment.

Late side effects developed in 1 (5%) patient (grade 2 gastrointestinal complication). Due to stage III EC this patient was subjected to WAI open field technique in 1999. Several months after completion of the treatment, after an error in nutrition, she complained of heavy constipation, which imposed the introduction of a strict hygienic-dietary regime and laxative medication. These complaints persisted during the whole period of the clinical observation and required the application of twice repeated colonoscopy (in 2004 and 2006) aiming at the detailed examination of the status of the colon. Deformed vascular outline was established as in chronic postradiation proctitis, with normal lumen, without injury and without active alterations as of the present moment. Till the end of the clinical observation the patient had persistent heavy constipation, requiring strict adherence to the dietary regime.

One patient with WAI in 1993 developed 6 years later an infraorbitally situated basal cell skin carcinoma.

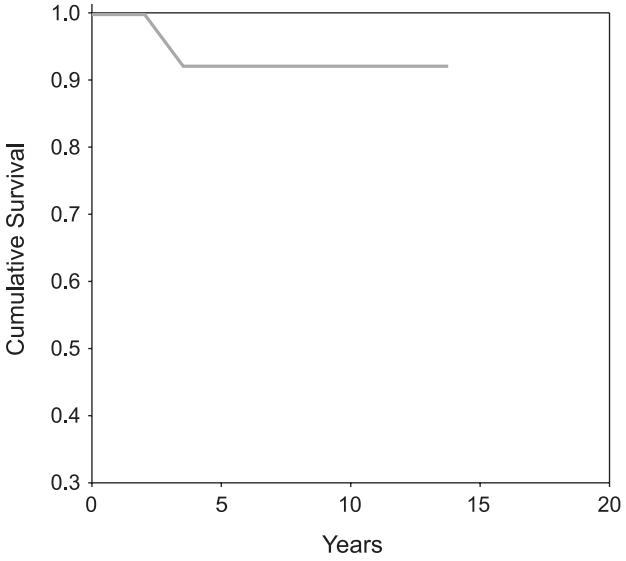

Figure 1. Overall survival of stage III endometrial cancer patients with whole abdominal irradiation.

Discussion

Chemotherapy, RT, or both have been added after surgery in an attempt to improve survival in patients with EC. However, the survival benefit to patients from such multimodality therapy remains uncertain. Despite the fact that retrospective reviews have documented pelvic failure rates ranging from 15 to 20% in patients with high-risk uterine-confined EC who have received no or inadequate RT, the role of RT has been questioned [14].

In high-risk EC patients the role of WAI as an adjuvant treatment carried out independently or in combination with CT has been an matter of investigation for decades. The treatment results achieved by means of WAI during the last decade of the past century are of the order of 35% 5-year OS [15]. Current authors continue the research to this direction and in the first years of the 21st century published papers report 3- and 5-year OS of 77 and 65% respectively in patients with stage IIIc EC [8-10]. The therapeutic potential of WAI applied either alone or combined with CT is also under investigation [14-17]. Results reported by GOG are of special interest in this respect with the randomization of 422 patients with stage III and IV EC treated with WAI or 7 courses of cisplatin/doxorubicin (AP) combination chemotherapy [18]. The hazard of death relative to WAI adjusted for stage was 0.67 (95% CI 0.51-0.89; $p < 0.01$) with a 11% predicted difference in the percent alive at 24 months (WAI: 59%, AP: 70%) in favor of CT, which was however accompanied with considerably higher toxicity.

The therapeutic results obtained by our single-institution study in patients with high-risk stage III EC are impressive (93% 5-, 10- and 14-year OS). These results are of the highest cited in the available to us literature (Table 2) [8,10,19,20].

Analysis of the OS in high-risk EC according to known single prognostic factors could not be carried out because of the small number of our cases and also because there was only one case with lethal outcome.

A number of other clinical studies investigate the impact of patient-, tumor- and treatment-related characteristics on the achieved therapeutic results in EC. Some authors determine the patient age as independent prognostic factor [8,14,21]. Using univariate analysis they prove that advanced age correlates with inferior disease-free survival (DFS) and local tumor control.

The impact of disease stage in EC is also a field of scientific interest and research by the international oncoradiological community [14,21,22]. For example, according to Greven et al. pathologic stage II patients had significantly worse DFS than stage I patients [14]. The attention of many authors is focused mainly in stage III patients, considering those with involved pelvic and/or paraaortic lymphatic chains (IIIC), as well as those with involved adnexa and/or positive cytology (IIIA, as were all of our patients) to be in particularly high-risk.

Table 2. Overall survival in patients with endometrial cancer

Overall survival		
%	*Years*	*Authors [Reference]*
53	5	Rose et al, 1992 [20]
75	5	Konski et al, 1996 [19]
72	5	Nelson et al, 1999 [10]
65	5	McMeekin et al, 2001 [8]
93	5 and 14	Present study

Among EC, uterine papillary serous carcinoma, which is accepted as the most aggressive variant of EC, occupies a special place. The majority of stage I patients have extrauterine dissemination during surgical treatment [23]. A significant part of patients recur after treatment in the abdomen, pelvis or vagina. The achieved survival rates are most often 35-50% for I - II and 0-15% for III - IV stage, respectively [24]. A number of present-day authors recommend WAI as an adjuvant treatment in all stages of the papillary serous carcinoma [24-27]. However, the highest therapeutic effect of WAI is observed in patients with early clinical stage of this tumor, with or without positive peritoneal cytology. Clear cell EC also is a matter of investigation concerning the therapeutic possibilities of WAI, with contradictory conclusions about its role so far [21,28].

In contrast to ovarian cancer, in the majority of the clinical studies of EC no prognostic impact of disease grade has been observed [8].

From the rest of EC characteristics, involved lymphatic chains and serosal involvement turn out as significant prognostic factors [9,22]. According to Ashman et al. patients with serosal involvement have considerably better survival than those with serosal and another extrauterine involvement (41.5%:20%, p=0.04) [22]. Issues of research are also bilateral adnexal involvement, capsular penetration of adnexal formation, presence of ascites or of dense adhesions between the tumor and pelvic organs. According to some authors positive peritoneal cytology together with involved lymphatic chains exerts considerable negative impact on OS and relapse-free survival (RFS) in EC [10].

Up until now there are some unclear points about whether the possibility of implementing optimal surgical treatment depends on certain biological tumor characteristics or is an independent prognostic factor *per se*. However, it is well known that the magnitude of residual disease is of prognostic importance in female malignant neoplasms.

In our study, only 2 patients had small-sized (< 2

cm) abdominal residual disease, 3 patients were with ascites and 4 with positive cytology. For this reason we were not able to prove the prognostic importance of these factors in our patient population.

At the background of the indisputable achievements of the multimodality treatments of malignant diseases, late complications emerge still more distinctly as one of the major problems of modern oncology. It is also especially important to take under consideration the late side effects of the performed treatment on the development of second primary malignancy. The mechanisms of carcinogenesis after multimodality treatments of patients with malignant neoplasms are complex and still poorly understood. On the basis of our modest experience we may summarize that the established acute and late toxicity, and second primary malignancy in the patients of our study, who were subjected to multimodal treatment, including also WAI open field technique, are similar with respect to frequency and clinical manifestation to those reported in the relevant literature [29-35].

We consider that at the present stage of development of the oncological practice, there is still no clear concept about the optimal therapeutic option for high-risk EC patients. When developing a therapeutic strategy for them, as well as for any new case of malignant neoplasm, optimal effectiveness with minimal early and late toxicity have to be sought for. WAI alone or as part of combined treatment is one treatment option that cannot be neglected.

We conclude that WAI achieves a most favorable 5- and 14-year survival rate with acceptable risk of acute and late side effects in properly selected patients with stage III EC. WAI alone or as part of combined treatment warrants further investigation in patients with high-risk EC.

References

1. Danon SH, Valerianova Z, Ivanova T (Eds). Bulgarian National Cancer Registry. Cancer incidence in Bulgaria 2004. AVIS-24 Ltd, 2007.
2. Dowdy S, Constantinou C, Hartmann L et al. Long-term follow-up of women with ovarian cancer after positive second-look laparotomy. Gynecol Oncol 2003; 91: 563-568.
3. Petit T, Velten M, d' Hombres A et al. Long-term survival of 106 stage III ovarian cancer patients with minimal residual disease after second-look laparotomy and consolidation radiotherapy. Gynecol Oncol 2007; 104: 104-108.
4. Skirnisdottir I, Sorbe B. Adjuvant radiotherapy in stage I-II epithelial ovarian cancer. Eur J Gynecol Oncol 2001; 22: 409-416.
5. Pakish B, Kohek P, Klug P et al. Treatment of primary cancer of the fallopian tube. Geburtshilfe-Frauenheilkd 1990; 8: 593-596.
6. Schafer U, Micke O, Witteler R et al. Radiotherapy in tubal carcinomas. Strahlenther Onkol 1996; 172: 205-210.
7. Potish RA, Twiggs LB, Adcock LL et al. Role of whole abdominal radiation therapy in the management of endometrial cancer; prognostic importance of factors indicating peritoneal metastases. Gynecol Oncol 1985; 21: 80-86.
8. McMeekin D, Lashbrook D, Gold M et al. Analysis of FIGO Stage IIIc endometrial cancer patients. Gynecol Oncol 2001; 81: 273-278.
9. McMeekin D, Tillmanns T. Endometrial cancer: treatment of nodal metastases. Curr Treat Opt Oncol 2003; 4: 121-130.
10. Nelson G, Randall M, Sutton G et al. FIGO stage IIIC endometrial carcinoma with metastases confined to pelvic lymph nodes: analysis of treatment outcomes, prognostic variables, and failure patterns following adjuvant radiation therapy. Gynecol Oncol 1999; 75: 211-214.
11. Arbruck SG, McClure J, Ivy SP et al. The common toxicity criteria manual. CTEP Website, http//ctep.info.nih.gov.
12. Cox JD, Stetz J, Pajak TF. 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: 1341-1346.
13. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53: 457-481.
14. Greven KM, Corn BW, Case D et al. Which prognostic factors influence the outcome of patients with surgically staged endometrial cancer treated with adjuvant radiation? Int J Rad Oncol Biol Phys 1997; 39: 413-418.
15. Genest P, Drouin P, Girard A et al. Stage III carcinoma of the endometrium: a review of 41 cases. Gynecol Oncol 1987; 26: 77-86.
16. Konsky A, Poulter C, Keys H et al. Absence of prognostic significance, peritoneal dissemination and treatment advantage in endometrial cancer patients with positive peritoneal cytology. Int J Rad Oncol Biol Phys1988; 14: 49-55.
17. Mundt A J, Murphy KT, Rotmensch J et al. Surgery and postoperative radiation therapy in FIGO Stage IIIC endometrial carcinoma. Int J Rad Oncol Biol Phys 2001; 50: 1154-1160.
18. Randall M, Brunetto G, Muss H. Whole abdominal radiation versus combination doxorubicin-cisplatin chemotherapy in advanced endometrial carcinoma. A randomized trial phase III of the Gynecologic Oncology Group. Proc Am Soc Clin Oncol 2003; 22: 2 (abstr).
19. Konski A, Domenico D, Irving D et al. Clinicopathologic correlation of DNA flow cytometric content analysis (DFCA), surgical staging, and estrogen/progesterone receptor status in endometrial adenocarcinoma. Am J Clin Oncol 1996; 19: 164-168.
20. Rose P, Cha S, Tak W et al. Radiation therapy for surgically proven para-aortic node metastasis in endometrial carcinoma. Int J Rad Oncol Biol Phys 1992; 24: 229-233.
21. Trope C, Kristensen GB, Abeler VM. Clear-cell and papillary serous cancer: treatment options. Res Clin Obstet Gynaecol 2001; 15: 433-446.
22. Ashman JB, Connell PP, Yamada D et al. Outcome of endometrial carcinoma patients with involvement of the uterine serosa. Gynecol Oncol 2001; 82: 338-343.
23. Sutton G, Axelrod J, Roy T et al. Adjuvant whole abdominal irradiation in clinical stages I and II papillary serous or clear cell carcinoma of the endometrium: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol 2006; 100: 349-354.

24. Sood BM, Jones J, Gupta S et al. Patterns of failure after the multimodality treatment of uterine papillary serous carcinoma. Int J Rad Oncol Biol Phys 2003; 57: 208-216.
25. Murphy J, Milosevic M, Chapman W et al. Uterine papillary serous carcinoma: evaluation of multimodality treatment with abdominopelvic radiotherapy and chemotherapy. Inter J Gynecol Cancer 2006: 16 (Suppl 1): 278-285.
26. Steed H, Manchul L, Rosen B et al. Uterine papillary serous carcinoma: evaluation of multimodality treatment with abdominopelvic radiotherapy and chemotherapy. Int J Gynecol Cancer 2006; 16: 278-285.
27. Mehta N, Yamada SD, Rotmensch J et al. Outcome and pattern of failure in pathologic stage I-II papillary serous carcinoma of the endometrium: implications for adjuvant radiation therapy. Int J Radiat Oncol Biol Phys 2003; 57: 1004-1009.
28. Murphy KT, Rotmensch J, Yamada SD et al. Outcome and patterns of failure in pathologic stages I-IV clear-cell carcinoma of the endometrium: implications for adjuvant radiation therapy. Int J Radiat Oncol Biol Phys 2003; 55: 1272-1276.
29. Small W Jr, Mahadevan A, Roland P et al. Whole-abdominal radiation in endometrial carcinoma: an analysis of toxicity, patterns of recurrence, and survival. Cancer J 2000; 6: 394-400.
30. Dembo AJ, Bush RS. Choice of postoperative therapy based on prognostic factors. Int J Rad Oncol Biol Phys 1982; 8: 893-897.
31. Dembo AJ. Abdominopelvic radiotherapy in ovarian cancer: a 10 year experience. Cancer 1984; 55: 2285-2290.
32. Dembo AJ, Davy M, Stenvig AE. Prognostic factors in patients with stage I epithelial ovarian cancer. Obstet Gynecol 1990; 75: 263-273.
33. Travis LB, Curtis RE, Boice-JD Jr et al. Second malignant neoplasm among long-term survivors of ovarian cancer. Cancer Res 1996; 56: 1564-1570.
34. Kaldor JM, Day NE, Kittelmann B et al. Bladder tumours following chemotherapy and radiotherapy for ovarian cancer: a case-control study. Int J Cancer 1995; 63: 1-6.
35. Dent S, Klaasen D, Pater J et al. Second primary malignancies following the treatment of early stage ovarian cancer: update of a study by the National Cancer Institute of Canada – Clinical Trials Group (NCIC-CTG). Ann Oncol 2000; 11: 65-68.