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Long-term morbidity of adjuvant whole abdominal radiotherapy (WART) or chemotherapy for early stage ovarian cancer

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ABSTRACT

The aim of the study was to evaluate long-term toxicity of adjuvant treatment in early stage ovarian cancer survivors. Data from all patients treated in one hospital for early stage ovarian cancer diagnosed between 1980 and 1990 were collected using a structured data form. In 93 FIGO stages I and II patients, cytoreductive and staging surgery was performed; 15 received no adjuvant treatment (controls), 39 whole abdominal radiotherapy (WART) and 39 platin-based chemotherapy. Median age at diagnosis was 54 years (range 21–83 years). During follow-up, 49/93 (53%) patients have died with a median overall survival of 18.4 years (95% CI 12.8–23.9). In both the radiotherapy and the chemotherapy group, 50% of patients reported long-term side-effects (all grades) versus 13% of controls. Two patients in the WART group died from bowel complications. Secondary malignancies were observed in 16 patients. Of all patients alive at the last follow-up, 12/17 (71%) patients treated with radiotherapy and 11/18 (61%) treated with chemotherapy experienced long-term morbidity versus 2/9 (22%) controls ($P = 0.03$).

In conclusion: Long-term follow-up of early stage ovarian cancer patients showed lasting GI morbidity in the survivors treated with adjuvant radiotherapy, which has therefore become obsolete. Cisplatin-based chemotherapy caused peripheral neuropathy versus virtual absence of problems in the survivors of just surgery, emphasising the need for strict criteria before instigating adjuvant treatment.

1. Introduction

The prognosis for early stage ovarian cancer is much more favourable than for advanced stage disease.[1] However, early stage patients who have undergone surgery frequently recur, and therefore various types of adjuvant therapies have been explored. In the 1980s, radiotherapy became popular for patients with little or no residual tumour after surgery following

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publications by Dembo et al.[2] His group showed survival that is to be improved by whole abdominal radiotherapy (WART). Apart from some dedicated clinics, most of the centres have later switched from radiotherapy to chemotherapy.[3–5] Nowadays, the consensus is that well-differentiated (grade 1) stages Ia and Ib ovarian cancer patients should be treated by optimal (staging) surgery, while other stages should receive chemotherapy.[5–7] Data from randomised studies, the ICON1 and the ACTION trials, show that platinum-based chemotherapy indeed improves survival in early stage ovarian cancer patients when compared to no adjuvant treatment.[8–10] However, some have argued that in the optimally staged patients the benefit of chemotherapy has not been proven.[9] According to the consensus statements, radiotherapy no longer has a place in the initial treatment. Despite this, however, radiotherapy is still advocated by some, and until recently randomised trials have been proposed.[11] In case radiotherapy and chemotherapy would prove to be equivalent, treatment-associated morbidity may influence the choice of (adjuvant) therapy. In our hospital, radiotherapy was abandoned as the first choice adjuvant treatment for patients with early stage ovarian cancer in 1996, as it was accompanied by severe gastrointestinal side-effects. However, peripheral sensory polyneuropathy, leukaemia and cardio-vascular events have been recognised after long-term follow-up for chemotherapy.[12–15] We are not aware of the studies comparing the long-term side-effects of radiotherapy with those of chemotherapy versus no treatment controls. Facilitated by a unique, single centre registry of gynaecologic cancer patients, started in the 1970s by dedicated clinicians, the underlying study aims to explore the long-term toxicity of adjuvant chemotherapy and adjuvant radiotherapy in early stage ovarian cancer patients.

2. Patients and methods

All patients with FIGO stage I/II ovarian cancer treated in the University Medical Centre Groningen from January 1980 to January 1990 were identified using the registries of the Departments of Radiotherapy and Gynaecologic Oncology. Hospital files as well as the electronic filing system that includes data since 1994 were used. When the follow-up was completed before 2000, the general practitioner of a patient was contacted and requested to fill out a questionnaire containing questions on actual status and regarding events during follow-up. Data that are collected included age at diagnosis and last follow-up, co-morbidity, date of surgery, stage, grade, details of surgery, the radiotherapy regimen and type of chemotherapy, and finally disease status and side-effects as reported during follow-up.

2.1. *Staging and treatment*

Prevailing regional guidelines for surgery in this period prescribed hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal biopsies and pelvic and para-aortic lymph node sampling. Adjuvant treatment was advised for all patients except for patients with stage Ia, well-differentiated ovarian carcinoma. For patients with stages I and II without residual tumour, radiotherapy was advised and for patients with residual tumour chemotherapy was preferred. Radiotherapy was administered according to a protocol devised by three Dutch university clinics (Utrecht, Amsterdam and Groningen).[16] The protocol comprised 23.75 Gy of whole abdominal radiotherapy (WART), in 19 fractions of 1.25 Gy daily for 5 days a week, followed by a pelvic boost (AP-PA technique) of 20 Gy in 10 daily fractions of 2 Gy. After 10 Gy the kidneys were shielded in the dorsal field. Adjuvant chemotherapy consisted of platinum-based polychemotherapy or monotherapy with melphalan, as age above 70 years and impaired renal function were considered a contraindication. Follow-up comprised visits once per 3 months in the first 3 years, once per 6 months in 4 and 5 years and annually from 5 to 10 years; follow-up often continued annually thereafter. Follow-up consisted of a gynaecologic examination, body weight, CA 125 serum level, laboratory (haemoglobin, ESR, liver and kidney function) and ultrasound on indication.

2.2. *Toxicity/adverse events*

Side-effects were graded based on the data available in the patients' charts, using the Common Terminology Criteria for Adverse Events version 3.0 (CTC-AE version 3.0).[17] We chose these criteria as they cover early as well as late side-effects due to both chemotherapy and radiotherapy. The use of this system nowadays is also supported by radiation oncologists.[18] All side-effects that developed at least 3 months or persisted after the completion of therapy were scored.

2.3. *Statistical analysis*

Analyses were performed using SPSS version 12.0. Non-parametric tests were used to check for differences between treatment groups. Survival curves were calculated according to the Kaplan Meier method. The cumulative incidence estimate, which takes competing risks into account, was used to depict the side-effects and secondary malignancies.[19]

3. Results

3.1. *Patients*

Between January 1980 and January 1990, 101 patients diagnosed with early stage ovarian cancer were treated. The files of 96 patients could be traced. Three patients were excluded from analysis; two patients received a combination of radiotherapy and chemotherapy as primary adjuvant treatment and for one patient no follow-up data were available. The study population therefore consisted of 93 patients. Patient characteristics are shown in Table 1. Patients who received no adjuvant treatment after surgery, all had FIGO stage I disease, well-differentiated tumours and were younger of age compared to the adjuvant treated patient group. Apart from one patient in the radiotherapy group with stage IIb and residual disease, patients left with residual disease received chemotherapy. Five patients did not undergo standard surgery. In one patient, 35 years old and presumably with FIGO stage Ic and pelvic adhesions, only one adnex was removed, followed by chemotherapy. In three young patients, two with FIGO IA and one IC, the uterus and one ovary were conserved

Table 1 – Patient Characteristics.

		Total $n = 93$	Observation $n = 15$	Radiotherapy $n = 39$	Chemotherapy $n = 39$
Age (years)	Median	54	39	56	53
	Range	21–83	21–80	22–73	23–83
Stage	Ia	36	14	12	10
	Ib	8	–	5	3
	Ic	19	1	8	10
	II	30	–	14	16
Grade	I	28	9	10	9
	II	25	2	11	12
	III	20	1	10	9
	Unknown	20	3	8	9
Residual tumour	None	79	14	38[x]	27[x]
	<2 cm	3	–	–	3
	>2 cm	2	–	–	2
	Size unknown	5	1	1	3
	Presence unknown	4	–	–	4
Type of surgery	TAH[a], BSO[b], omentectomy	44	4	11	29
	Same + lymphadenectomy	44	7	28[y]	9
	Other	5	4	0	1

a TAH = total abdominal hysterectomy.
b BSO = bilateral salpingo-oophorectomy.
x Significant difference $P = 0.01$
y Six patients from this group needed surgery for intestinal obstruction and four were treated conservatively for gastro-intestinal complications (10/28) versus one patient from the group without lymphadenectomy (1/11).

as they wished to start a family; they did not receive adjuvant treatment. Finally, in a 62 years old patient with FIGO stage IA disease and a metastatic carcinoid tumour, just a bilateral salpingo-oophorectomy was performed. She died due to the carcinoid tumour, 10.4 years after the surgery for the ovarian cancer.

Chemotherapy was cisplatin-based in 24 patients; carboplatin-based in four and consisted of melphalan in 11 patients. The subgroup receiving melphalan ($n = 11$) had a median age of 63 years (range 54–83) versus 50 years (range 23–64) for the subgroup receiving polychemotherapy (Mann Whitney U: $P < 0.001$).

3.2. *Follow-up*

Median follow-up of surviving patients was 18.9 years (range 3.3–25.3 years). During follow-up, 49 of 93 patients died (53%). The general practitioners of 48 patients, whose follow-up was incomplete, were asked for information; of which the follow-up of 6 patients remained incomplete. The median follow-up in these six patients was 7.4 years (range 3.3–17 years).

3.3. *Overall and disease-specific survival*

For the whole group, median survival was 18.4 years (95% confidence interval (CI) 12.8-23.9). Overall 5-year survival was 74%, 10-year survival 62%, 15-year survival 56% and 20-year survival 46%. As patients did not randomly receive adjuvant treatment, survival curves of the subgroups are only shown as the characteristics of the treatment groups (Fig. 1a overall survival; Fig. 1b disease-specific survival). Ten-year overall survival was 65% in the group without adjuvant treatment, 60% in the radiotherapy group and 62% in the chemotherapy group. Median overall survival was 19.6 years (CI 9.5–29.6) in the chemotherapy group, 17.3 years (CI 14.0–20.5) in the radiotherapy group and was not reached for the group receiving no adjuvant treatment.

3.4. *Secondary malignancies*

Other malignancies occurred before, simultaneously and after primary ovarian cancer treatment. In 25 patients, 29 other malignancies were diagnosed. Five of these tumours, four breast cancers and one carcinoid tumour of the small intestines, were diagnosed before ovarian cancer. Also, 5 tumours

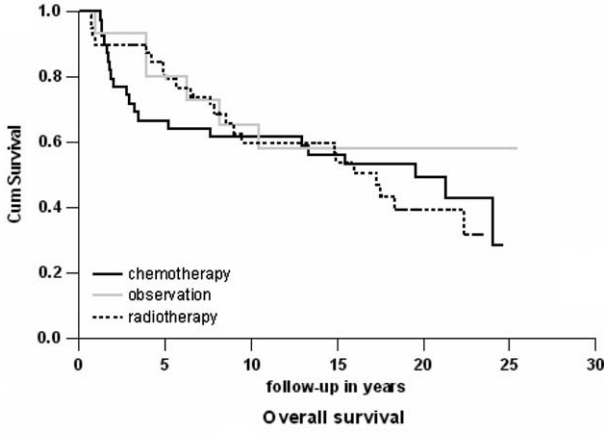

Fig. 1a – Overall survival of the three treatment groups.

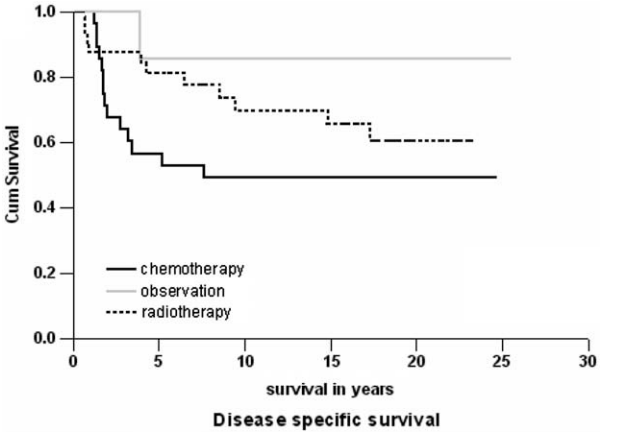

Fig. 1b – Disease-specific survival of the three treatment groups.

were diagnosed concurrently; 4 endometrial cancers and 1 Hodgkin's lymphoma, and 19 tumours were detected after treatment. Table 2 shows the origin of these 19 tumours during follow-up. The median time from the diagnosis of ovarian cancer to the occurrence of these tumours was 16.3 years (range 3.5–22.9). In the radiotherapy and in the chemotherapy group, 7 patients developed one or more secondary malignancies, as did 2 patients in the group not receiving any adjuvant therapy. Five of 9 secondary malignancies found in the radiotherapy group were located in the irradiated abdomen (3 colon, one pancreatic and a cholangiocarcinoma). In the chemotherapy group, three of eight malignancies also had an abdominal localisation (colon, rectum and bladder, respectively).

3.5. *Side-effects*

Table 3 shows the long-term side-effects experienced by the patients, which are (possibly) related to the adjuvant therapy. Patients who received radiotherapy especially suffered from gastro-intestinal symptoms, while patients who received chemotherapy more often showed peripheral sensory neuropathy. In total, there were 19 patients experiencing 43 side-effects (all grades) in the radiotherapy group and 19 patients with together 30 side-effects (all grades) in the chemotherapy group compared to just 2 patients with 2 side-effects in the observation group ($P = 0.01$).

3.6. *Cumulative numbers*

Fig. 2a shows the cumulative incidence of side-effects in the different treatment groups, adjusted for competing risks. Death is such a competing risk. In this analysis, the date of incidence of the first side-effect or toxicity such as neuropathy was used. Fig. 2b shows the cumulative incidence of secondary tumours.

Of patients alive at the last follow-up, 12/17 (71%) patients treated with radiotherapy and 11/18 (61%) treated with chemotherapy have experienced long-term morbidity versus 2/9 (22%) controls (combined testing 23/35 (66%) versus 2/9; $P = 0.03$).

Follow-up of these three3 patient groups still alive at the last follow-up was comparable (median 18.5, 19.9 and 18.9 years); however, age at diagnosis and thus at the last follow-up widely differed. Status at the last follow-up is illustrated in Table 4. As shown, at this last follow-up, just 5/17 (29%) patients treated with radiotherapy and 5/18 (28%) treated with chemotherapy have neither experienced an adverse event nor a secondary malignancy versus 7/9 (78%) controls (combined tested 10/35 (29%) versus 7/9 (78%) controls ($P = 0.02$)).

3.7. *Gastro-intestinal side-effects*

In 6 patients (15%), surgery was indicated for radiation enteritis, four of whom suffered from bowel obstruction. Two of them eventually died of gastro-intestinal complications. None of the patients who were surgically treated for radiation enteritis had a total colectomy (removal of total organ = grade 4). Therefore, in the four remaining patients and in one conservatively treated patient, the event was scored as grade 3. Four additional radiotherapy patients suffered from moderate gastro-intestinal side-effects but could be conservatively treated. In all, 11/39 (28%) of patients who received radiotherapy had long-term gastro-intestinal side-effects. One patient

Table 2 – Secondary malignancies after completion of therapy, according to therapy group.

Tumour type	Observation $n = 15$	Radiotherapy $n = 39$	Chemotherapy $n = 39$
Breast		2[a]	2
Lung	1	1	
Stomach sarcoma			1
Pancreas		1	
Gallbladder		1	
Bladder	1		1
Colon		3	1
Rectum			1
Skin, non-melanoma			3[b]
Total	2	8 (7 patients)	9 (7 patients)

a One patient developed lung cancer 4 years later as well.
b Two patients also developed breast and colon cancer, respectively.

Table 3 – Grading of side-effects according to CTC version 3.0.; several categories can be scored per patient.

Category		Grade	Controls $n = 15$	Radiotherapy $n = 39$	Chemotherapy $n = 39$
Cardiac	Hypertension	2	1	2	5
	Angina	3	1	1	–
	Heart failure	4	–	1	–
Vascular	Raynaud	2	–	1[b]	1
	Deep venous thrombosis	3	–	1	–
	Leg ischaemia requiring amputation	4	–	2	–
Haemorrhage	CNS	5		1	
Gastro-intestinal	Chronic diarrhoea	2	–	4	–
	Radiation enteritis	3	–	5	1
		5		2[a]	
Hepatobiliary		3	–	–	1
Renal/genitourinary	Cystitis	2	–	2	–
	hydronephrosis	3	–	–	1
	Renal insufficiency	4	–	2	–
Sexual function		2	–	2	–
Neurologic	Sensory	2	–	1	13
	Neuropathy	3	–	–	1
	Ischaemic stroke	4	–	1	2
Auditory	Hearing loss	2	–	–	1
		1	–	1	–
Musculoskeletal Complaints	Osteoporosis	2	–	2	–
	Fractures	3	–	2	2
Lymphatics	Peripheral oedema	1	–	1	–
		2	–	3	1
Skin	Pruritus	2	–	–	1
Blood	Anaemia	2	–	3	–
Pain		2	–	3	–
Total			2	43	30

a Two patients eventually died; their cases are described in the text.
b After chemotherapy for recurrent disease.

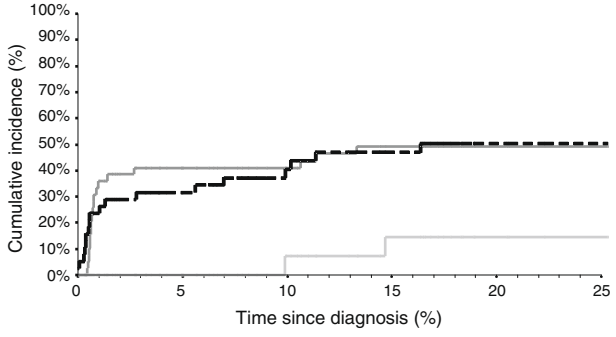

Fig. 2a – Cumulative incidence of long-term side-effects in the study population. Observation: light-grey line; radiotherapy: black dotted line; chemotherapy: dark-grey line.

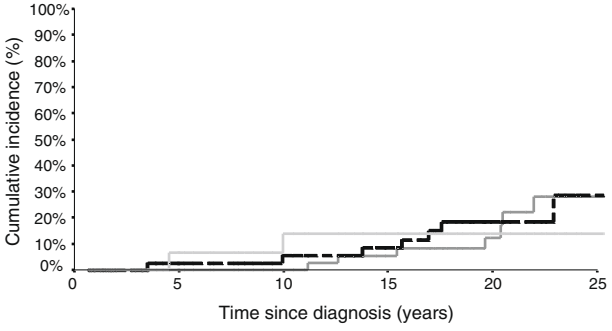

Fig. 2b – Cumulative incidence of secondary malignancies in the study population. Observation: light-grey line; radiotherapy: black dotted line; chemotherapy: dark-grey line.

who died of complications was 57 years old and diagnosed with ovarian cancer FIGO stage Ia, grade 3. She suffered from a short bowel syndrome after surgery and severe enteritis and died 9.6 months later of urosepsis. The other patient also had a short bowel syndrome after surgery and eventually died, 72 years old, of hepatic failure while on total parental nutrition, 9.4 years after being diagnosed with ovarian cancer. The patients diagnosed with and treated for radiation enteritis that survived, all had lifelong side-effects for which they used dietary measures, oral loperamide and iron. In 10 of 11 patients suffering from gastro-intestinal side-effects, including the 6 patients who had additional surgery for bowel problems, the pelvic and/or para-aortic lymph nodes had been removed during primary surgery for staging purposes. In the chemotherapy group, one patient underwent surgery for an obstructed bowel 23.5 years after primary surgery. The obstruction was caused by adhesions, which may have been due to the primary surgery.

Table 4 – Patients alive at last follow-up.

Alive at last follow-up	Observation, *n* (%) 9 (60)	Radiotherapy, *n* (%) 17 (42)	Chemotherapy, *n* (%) 18 (45)
Age in years (median)	45	71	69
Range	35–67	39–88	44–92
Follow-up in years (median)	18.9	18.5	19.9
Range	5–25	3–23	11–24
Healthy and NED	7	5	5
Long-term morbidity	2	12	11
Secondary malignancy	1	2	5

3.8. *Cardio-vascular side-effects*

Table 3 also shows the cardio-vascular side-effects in detail. All side-effects were included only when appearing for more than 3 months after the completion of treatment. There are eight side-effects in the radiotherapy group and six in the chemotherapy group (especially hypertension) versus two in the observation group. One of the patients in the radiotherapy group was subsequently treated with chemotherapy for recurrent disease and developed Raynaud's phenomenon. The patient in the radiotherapy group that suffered from a pulmonary embolus later died of intracranial haemorrhage while on anticoagulation therapy.

3.9. *Neurological side-effects*

Peripheral sensory neuropathy did not disturb the activities of daily living (ADL), grade 2. Two elderly patients in the chemotherapy group suffered from an ischaemic stroke (grade 4) as did one patient in the radiotherapy group. One of the patients with an ischaemic stroke had received melphalan, but all peripheral neuropathy occurred in patients after cisplatinum. Only 4 patients were treated with carboplatin; and of the 24 patients treated with cisplatin, 12 (50%) still complained of peripheral sensory neuropathy after a median of 5.7 years (range 5 months to 17 years).

4. Discussion

This study with a unique, long follow-up shows long-term morbidity in 66% of survivors, who received adjuvant treatment. Early stage ovarian cancer has a relatively good prognosis with a 5-year survival of more than 80%. As these women often are diagnosed at a relatively young age, even late complications occurring 15 or 20 years after initial treatment, such as secondary malignancies or vascular disease, should be taken into account when choosing a treatment modality. However, most of the follow-up studies in patients with malignancies concentrate on the relatively short-term results presenting 3, 5 or incidentally 10-year survival figures. Moreover, in clinical practice follow-up is often discontinued 5 or 10 years after diagnosis, as the chance of recurrence is then almost zero, and most of the patients are considered to be cured. Long-term follow-up data as presented in the current study are therefore scarce but essential in appreciating the long-term impact of different treatment modalities.

In a review on adjuvant therapy in early stage ovarian cancer, Winter-Roach et al. concluded that the studies comparing radiotherapy with chemotherapy did not show an advantage for one or the other as far as survival was concerned, albeit chemotherapy was not as optimally dosed as it is nowadays.[5] Skirnisdotter et al. evaluated the data of 215 ovarian cancer patients treated with adjuvant radiotherapy and concluded that radiotherapy was not superior to chemotherapy.[20] The survival rates as observed in our study population (overall 5-year survival 74% and 10-year survival 62%) are quite comparable to those found by others in the early stage ovarian cancer patients diagnosed and treated in the same time period.[21,22]

The CTC-AE version 3.0 that was used in our study allows the comparison of side-effects of different treatment modalities and both events due to chemotherapy and radiotherapy. A flaw in our study is that side-effects were not prospectively registered. However, this flaw applies for all patient groups equally and therefore does not hamper cross-comparison. Retrospective scoring will always lead to the underestimation of the real burden for the patients. In 50% of patients receiving radiotherapy or chemotherapy, we observed side-effects versus just 13% in the group treated solely with surgery. Moreover, of patients still alive at the last follow-up, 66% of patients who received adjuvant therapy experienced side-effects versus 22% of controls. However, age may bias these results, as our controls were younger and side-effects such as hypertension and secondary malignancies will strongly increase with age.[23]

Furthermore, for adequately judging the impact of adverse events, it is important to take into account the actual number of patients still alive. The cumulative incidence estimate used in the present study takes into account competing risks and seems an appropriate instrument.[19] However, as death is a competing risk, figures on the side-effects might seem pleasantly low, while in reality this might be the consequence of a high death rate. Some therefore advocate actuarial estimates, but these will tend to overestimate late complications.[24,25]

Gastro-intestinal problems appeared to be high (7 of 39 (18%) patients treated with radiotherapy) and severe, as the number of patients in need of surgery, 6/39 (15%), is high compared to other studies (Table 5). It was suggested that retroperitoneal lymph node dissection may cause more adhesions and less small bowel mobility exposing the bowel to radiation damage.[16] Indeed, 10/11 patients with severe gastro-intestinal complications underwent retroperitoneal lymph node dissection. Finally, 24 of 28 patients were treated

Table 5 – Bowel toxicity after adjuvant radiotherapy in ovarian cancer.

Study	FIGO stage	*n*	Adjuvant radiotherapy	Follow-up median + range (years)	Bowel toxicity (%)	Bowel surgery (%)
[20]	IA–IIC	132 83	Lower abdomino-pelvic WART	8.7 4.8–22	12 13	3 8.4
[22]	I–III	94	WART followed by melphalan	24 21–29	12	9
[27]	I–III	71	WART, in 31 + CTX[a]	4.8 0.2–23	21	11
[3]	I–III	1068	WART	?	?	5.6
Present study	I–II	39	WART	18.5 3.3–23	18	15

a CTX = chemotherapy: L-PAM or cyclophosphamide (and cisplatin in two pts).

with cisplatin resulting in a high frequency of sensory neuropathy. Nowadays, carboplatin as the standard platinum compound in most of the regimens has no neurological side-effects.[26] Combination with paclitaxel may modify this advantage to some extent, but polyneuropathy after taxoids will be less severe and long lasting than that after cisplatin.

In the present study, new malignancies were diagnosed in 16/93 patients (17.2%) which is comparable to the cumulative risk at 20 years of 18.4% found by Travis et al. in a group of 32,251 women with ovarian cancer, including 4,402 10-year survivors. For comparison, the population expected risk of secondary malignancies for their group was only 11.5% at 20 years.[13] They observed significantly increased risks for all solid tumours and leukaemia; following radiotherapy alone, excess of solid tumours increased with time, while after chemotherapy the risk was significantly elevated only within a 5–9 year interval. Patients surviving more than 15 years following radiotherapy experienced excess malignancies of the pancreas, the bladder, the rectum and the connective tissue within a background of almost twice as many solid tumours as expected.

As a significant proportion of early stage ovarian cancer patients will survive, long-term morbidity becomes more relevant. In subgroup analyses in the ACTION trial, that studied 448 early stage ovarian cancer patients randomised to adjuvant chemotherapy or control, no survival benefit of chemotherapy was found in the small group of patients who were optimally staged.[9] For the future, a trial prospectively studying adjuvant chemotherapy in optimally staged patients was suggested.

In conclusion, we found the majority of patients surviving early stage ovarian cancer, suffering from long-term morbidity related to the adjuvant treatment. As survival has not been found superior after radiotherapy, which induces more severe toxicity i.c. radiation enteritis, in our opinion radiotherapy has no place any more. The substitution of cisplatin by carboplatin will largely forego peripheral neuropathy. The advantages of any adjuvant treatment in terms of survival, however, should be carefully weighed against eventual long-term morbidity.

Conflict of interest statement

None declared.

REFERENCES

1. Cannistra SA. Cancer of the ovary. *New Engl J Med* 2004;**351**:2519–29.
2. Dembo AJ, Bush RS, Beale FA, et al. The Princess Margaret Hospital study of ovarian cancer: stages I, II, and asymptomatic III presentations. *Cancer Treat Rep* 1979;**63**:249–54.
3. Dembo AJ. Epithelial ovarian cancer: the role of radiotherapy. *Int J Radiat Oncol Biol Phys* 1992;**22**:835–45.
4. Cardenes H, Randall ME. Integrating radiation therapy in the curative management of ovarian cancer: current issues and future directions. *Semin Radiat Oncol* 2000;**10**:61–70.
5. Winter-Roach B, Hooper L, Kitchener H. Systematic review of adjuvant therapy for early stage (epithelial) ovarian cancer. *Int J Gynecol Cancer* 2003;**13**:395–404.
6. Thigpen T. First-line therapy for ovarian carcinoma: what's next? *Cancer Invest* 2004;**22**(Suppl. 2):21–8.
7. Bookman MA. Standard treatment in advanced ovarian cancer in 2005: the state of the art. *Int J Gynecol Cancer* 2005;**15**(Suppl. 3):212–20.
8. Trimbos JB, Parmar M, Vergote I, et al. International Collaborative Ovarian Neoplasm trial 1 and Adjuvant ChemoTherapy in Ovarian Neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. *J Natl Cancer Inst* 2003;**95**:105–12.
9. Trimbos JB, Vergote I, Bolis G, et al. Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European Organisation for Research and Treatment of Cancer-Adjuvant ChemoTherapy in Ovarian Neoplasm trial. *J Natl Cancer Inst* 2003;**95**:113–25.
10. Colombo N, Guthrie D, Chiari S, et al. International Collaborative Ovarian Neoplasm trial 1: a randomized trial of adjuvant chemotherapy in women with early-stage ovarian cancer. *J Natl Cancer Inst* 2003;**95**:125–32.
11. Hepp R, Baeza MR, Olfos P, Suarez E. Adjuvant whole abdominal radiotherapy in epithelial cancer of the ovary. *Int J Radiat Oncol Biol Phys* 2002;**53**:360–5.
12. Kaldor JM, Day NE, Pettersson F, et al. Leukemia following chemotherapy for ovarian cancer. *New Engl J Med* 1990;**322**:1–6.
13. Travis LB, Curtis RE, Boice Jr JD, et al. Second malignant neoplasms among long-term survivors of ovarian cancer. *Cancer Res* 1996;**56**:1564–70.
14. Meinardi MT, Gietema JA, van der Graaf WT, et al. Cardiovascular morbidity in long-term survivors of metastatic testicular cancer. *J Clin Oncol* 2000;**18**:1725–32.

15. de Vos FY, Nuver J, Willemse PH, et al. Long-term survivors of ovarian malignancies after cisplatin-based chemotherapy; cardiovascular risk factors and signs of vascular damage. *Eur J Cancer* 2004;**40**:696–700.
16. van Bunningen B, Bouma J, Kooijman C, et al. Total abdominal irradiation in stage I and II carcinoma of the ovary. *Radiother Oncol* 1988;**11**:305–10.
17. DCTD NND. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0. 12.12.2003.
18. Chen Y, Trotti A, Coleman CN, et al. Adverse event reporting and developments in radiation biology after normal tissue injury: International Atomic Energy Agency consultation. *Int J Radiat Oncol Biol Phys* 2006;**64**:1442–51.
19. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med* 1999;**18**:695–706.
20. Skirnisdottir I, Nordqvist S, Sorbe B. Is adjuvant radiotherapy in early stages (FIGO I–II) of epithelial ovarian cancer a treatment of the past? *Oncol Rep* 2005;**14**:521–9.
21. Raymond E, Drolet Y, Marpeau L, et al. Long-term follow-up after adjuvant chemotherapy in completely resected early stage ovarian carcinoma. *Eur J Obstet Gynecol Reprod Biol* 1997;**72**:181–90.
22. Dusenbery KE, Bellairs EE, Potish RA, Twiggs LB, Boente MP. Twenty-five year outcome of sequential abdominal radiotherapy and melphalan:implications for future management of epithelial carcinoma of the ovary. *Gynecol Oncol* 2005;**96**:307–13.
23. Ong KL, Cheung BM, Man YB, Lau CP, Lam KS. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999–2004. *Hypertension* 2007;**49**:69–75.
24. Bentzen SM, Vaeth M, Pedersen DE, Overgaard J. Why actuarial estimates should be used in reporting late normal-tissue effects of cancer treatment ... now! *Int J Radiat Oncol Biol Phys* 1995;**32**:1531–4.
25. Maduro JH, Pras E, Willemse PH, de Vries EG. Acute and long-term toxicity following radiotherapy alone or in combination with chemotherapy for locally advanced cervical cancer. *Cancer Treat Rev* 2003;**29**:471–88.
26. The International Collaborative Ovarian Neoplasm (ICON) Group. Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial. *Lancet* 2002;**360**:505–15.
27. Firat S, Murray K, Erickson B. High-dose whole abdominal and pelvic irradiation for treatment of ovarian carcinoma: long-term toxicity and outcomes. *Int J Radiat Oncol Biol Phys* 2003;**57**:201–7.