OVERVIEW ARTICLE

Taylor&Francis healthsciences

A Systematic Overview of Radiation Therapy Effects in Ovarian Cancer

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Acta Oncologica Vol. 42, No. 5/6, pp. 562–566, 2003

A systematic review of radiation therapy trials in several tumour types was performed by The Swedish Council of Technology Assessment in Health Care (SBU). The procedures for evaluation of the scientific literature are described separately (Acta Oncol 2003; 42: 357–365). This synthesis of the literature on radiation therapy for ovarian cancer is based on data from six randomized trials. Moreover, data from one prospective study and three retrospective studies were used. In total, 10 scientific articles are included, involving 1 282 patients. The results were compared with those of a similar overview from 1996 including 15 042 patients. The conclusions reached can be summarized in the following points:

- There is no scientific documentation supporting adjuvant radiotherapy for early-stage, low-risk patients.
- No studies have been reported where adjuvant radiotherapy has been compared with no adjuvant therapy in early-stage, high-risk patients.
- Adjuvant radiotherapy, either whole abdominal irradiation or intraperitoneal p^{32}, has been compared with adjuvant chemotherapy in early-stage, high-risk patients. There is no scientific evidence to show that there is a difference in efficacy.
- There is some evidence to suggest that adjuvant radiotherapy after radical surgery leads to an increase in disease-free survival rate for patients with advanced-stage ovarian cancer.
- There is little documentation on long-term side effects (second malignancy) after adjuvant radiotherapy and no conclusions can be drawn.

Received 7 May 2003
Accepted 3 June 2003

In the year 2000, 826 new cases of ovarian cancer were diagnosed in Sweden making it the fifth most common cancer in women. The median age of newly diagnosed patients was between 65 and 69 years. The Nordic countries have the highest incidence of ovarian cancer in the world. According to the latest results from the Cancer Registry of Sweden, the 5-year survival rate for all stages was 36.5% for women diagnosed between 1964 and 1966 and 44.6% for women diagnosed between 1993 and 1996.

Histologically, ovarian cancer is divided into many prognostically important subtypes. Epithelial tumours represent the largest group (95%) of all ovarian malignancies. The following literature review is limited to this group. The degree of differentiation is the most important prognostic factor and well-differentiated tumours have the best prognosis.

Staging is based on the 1986 system FIGO (International Federation for Gynaecology and Obstetrics). Stages IA–IIA are considered to belong to the group of early tumours, as they are confined to the gynaecological organs; the advanced stages IIB–III are spread outside gynaecological organs as well as in the abdomen and stage IV outside the abdominal cavity.

Tumour stage is very important in treatment and prognosis. Tumour symptoms tend to be vague; hence ovarian cancer is often detected late. Approximately two-thirds of all ovarian cancer cases are diagnosed after the disease has spread beyond the genital organs.

The treatment of ovarian cancer has undergone several developments. During the 1950s, surgery and radiotherapy

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 ISSN 0284-186X
DOI: 10.1080/02841860310014426

were the dominant treatment modalities. Since the introduction of chemotherapy during the late 1950s and its demonstrated effect in advanced ovarian cancer (1), radiotherapy has lost importance and has been increasingly abandoned. It is difficult to deliver adequate radiation doses to the upper abdomen, where the radiosensitivity of the kidney and the liver is the limiting factor. The development of chemotherapy has also influenced the approach of surgical treatment. Standard treatment of ovarian cancer today is primary debulking surgery with maximum reduction of tumour volume, which is often followed by intensive chemotherapy, especially in advanced tumours.

SUMMARY OF THE EARLIER REPORT, SBU 129/2

The synthesis of the literature on radiotherapy in the earlier SBU report 129/2 is based on 74 scientific publications including 12 randomized studies, 18 prospective studies, 36 retrospective studies and 8 others. These studies include 6 140 patients.

Conclusions

Treatment for patients with early stages of ovarian cancer (stage IA and IIA) is surgery. The value of adjuvant treatment, i.e. chemotherapy and radiotherapy is not demonstrated.

Tumour volume is decisive to the success of radiotherapy. Microscopic or small macroscopic cancer residuals, remaining after surgery, may respond to radiotherapy, thereby promoting survival.

The importance of radiotherapy for advanced ovarian cancer is controversial, and studies frequently show contradictory results.

Two studies have shown the favourable role played by radiotherapy in consolidation treatment of patients if they become cancer free at advanced stages.

The role of radiotherapy in treating large volumes of residual cancer has not been demonstrated, except for strictly palliative treatment.

Discussion

The earlier report evaluated the literature until 1994 and the main conclusion was that value of radiotherapy or chemotherapy as adjuvant treatment in the early stages was not demonstrated. Radiotherapy as consolidation after surgery and chemotherapy might be of value in advanced tumour stages, but only two studies were performed. The general conclusion regarding advanced stages was that large tumour volumes are technically difficult to treat.

Literature

The articles on which the conclusions in the SBU 129/2 report were based were classified and graded as follows (number of studies/number of patients)

	1 = High	2 = Moderate	3 = Low	Total
M	–	–	–	–
C	3/684	3/384	6/409	12/1 477
P	8/220	6/244	4/18	18/462
R	9/3 045	5/160	22/653	36/3 858
L	3	–	–	3
O	3	2/343	–	5/343
Total	26/3 949	16/1 111	32/1 080	74/6 140

M = meta-analysis; C = controlled clinical trial; P = prospective trial; R = retrospective study; L = literature review; O = other studies.

ASSESSMENT OF NEW LITERATURE

Search method and selections

Computerized literature searches were carried out in Medline for 1994-October 2001. The MeSH search term 'ovarian neoplasms' was used in combination with radiotherapy as a subheading, the MeSH-term and text word. Limitations to the following study designs were made: randomised, controlled studies, other controlled studies, meta-analysis, epidemiologic studies such as case-control studies, cohort studies, prospective studies and retrospective studies. A supplementary search was made in the Cochrane Library.

Initially, 51 Abstracts on ovarian cancer were received. Reasons for exclusion of 43 Abstracts and publications not selected for further analysis were:

Group		
A	5	Reviews
B	13	Basic science and experimental phase I–II investigations
C	15	Studies with small patient material
D	10	General topics not relevant to the aim of the study

Of 10 publications analysed, 6 represent randomized clinical trials. One Abstract with unpublished data also represents a randomized trial (2).

OVERVIEW OF NEW STUDIES

Early stages (Ia–IIc) postoperative treatment

See Overview 1 for a description of the trials, trial results and conclusions. The literature shows that:

- The main treatment for patients with early-stage ovarian cancer (stages IA–IIA) is surgery.
- The value of adjuvant radiotherapy has not been demonstrated. Only one small, randomized trial is reported, in which surgery alone is compared with surgery plus adjuvant RT.

Overview 1

Ovarian cancer. Early stages (Ia–IIc), postoperative treatment

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results			Conclusion/comments
Dent 2000 (4) C	Comparison between different adj treatments A: Surgery + WAR, 22.5 Gy/10 fr B: Surgery + adj CHT C: Surgery + p32 IP CHT = melphalan	1975–1984 St Ia–IIa, IIb, IIIa A: 107 pts B: 106 pts C: 44 pts (closed early due to toxicity)	Follow-up median 13.5 y A B C	OS% 45 49 50 ns	DFS% 50 62 51 ns	Second malignancies: sign, increase compared to age-matched population. No sign. difference between treatment groups. C2
Young 1999 (2) C	CHT vs. isoptope RT as adj treatment A: Surgery + p32 IP B: Surgery + adj CHT CHT = cyclophosphamide + cisplatin	1986–1994 St I–IIa high risk (grade 2, 3) A: 98 pts B: 107 pts	Follow up median 5 y A B	DFS% 66 77 ns		No difference in DFS between groups. Two pts with bowel perforation in gr A. Abstract
Bolis 1995 (3) C	Value of adj CHT in low-risk pts I. Low-risk early stages A: Surgery + adj CHT B: Surgery CHT vs. isotope RT as adj treatment in high-risk pts II. High risk early stages A: Surgery + adj CHT B: Surgery + p32 IP CHT = cisplatin	1983–1990 I. St Ia–Ib, grade 1–3 A: 41 pts B: 42 pts II. St Iaii–bii, Ic*, grade 1–3 A: 77 pts B: 75 pts	Follow-up median 5 y I A B II A B	OS% 88 82 ns 81 79 ns	DFS% 83 65 p = 0.06 85 65 p = 0.008	Significantly better DFS but not OS for high-risk early stages treated with surgery + CHT compared with surgery + p32. Low power. C3
Chiara 1994 (5) C	CHT vs. RT as adj treatment in high-risk, early-stage pts A: Surgery + adj CHT B: Surgery + WAR, 43.2 Gy to pelvis, 30.2 Gy to abdomen. Open field technique. CHT = cisplatin + cyclophosphamide	1985–1989 St I–II, grade 2, 3 A: 36 pts B: 34 pts	 A B Diarrhoea (WHO gr 3–4) 28% in gr B. One late bowel obstruction in gr B	OS% 71 53 ns	RFS% at 5 y 74 50 ns	No difference in OS or RFS between surgery + adjuvant CHT and surgery + adjuvant RT. Small material. Large Protocol violation for radiotherapy because of patient–doctor decision (44 pts treated with CHT and 25 with WAR). C3

*Iaii = tumour limited to one ovary, no ascites. Tumour on external surface of capsule and/or rupture.
Ibii = tumour in both ovaries, no ascites. Tumour on external surface of capsule and/or rupture.
Ic = Ia or Ib with ascites or positive washings.
Abbreviations: adj = adjuvant; CHT = chemotherapy; DFS = disease-free survival; IP = intraperitoneal; NR = not reported; ns: not significant; OS-overall survival; pts = patient(s); WAR = whole abdominal radiation; RT = radiotherapy.

– In one study, adjuvant chemotherapy with cisplatin in early stages of high-risk patients (stages Iaii–Ibii, grade 1–3) gave significantly better DFS ($p = 0.008$) but not OS, compared with radiotherapy given intraperitoneally with P^{32}. When adjuvant chemotherapy was compared with external beam radiation to whole abdomen, no difference with respect to disease-free or overall survival could be found.

Advanced stages (IIIa–IVb) postoperative treatment

See Overview 2 for a description of the trials, trial results and conclusions. The literature shows that:

– All reported studies are small, with less than 100 patients (2 studies) or less than 50 patients (3 studies) in each treatment group.

– In patients with advanced ovarian cancer with a pathologically complete response after chemotherapy, radiotherapy seems to play a role as consolidation therapy.

Radiotherapy in palliative treatment

See Overview 3 for a description of the trials, trial results and conclusions. The literature shows that:

– Radiotherapy can be used for the relief of symptoms.

LITERATURE

The articles on which the conclusions in this report were based were classified and graded as follows (number of studies/number of patients):

Overview 2

Ovarian cancer. Advanced stages—postoperative treatment

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results	Conclusion/comments
Einhorn 1999 (7) R Case control	CHT vs. CHT+RT as adj treatment A: Surgery+CHT+WAR 40 Gy B: Surgery+CHT 6 field RT technique	St IIb–IV A: 75 pts (1976–1984) B: 98 pts (1991–1992)	DFS% at 5 y A: 29.3 B: 12.2 p = 0.001	Significantly better DFS with RT+CHT compared with CHT alone after surgery for advanced ovarian cancer. New technique of RT with homogeneous doses to almost whole abdomen. In 15% of patients interruption of treatment due to haematological toxicity. R3
Fyles 1998 (10) C	Different doses of adj RT A: Postop WAR 22.0 Gy/22 fr B: Postop WAR 27.5 Gy/27 fr Boost to 22.5 Gy in both groups. In both groups optimal debulking surgery was performed	1981–1990 St I–III A: 67 pts B: 58 pts	OS% DFS% at 5 y A 83 74 B 72 ns 67 ns	No difference in survival, tumour control or toxicity between high- and low-dose RT. Underpowered trial. C3
Nicholson 1998 (11) Case control study P	Value of adj RIT Induction CHT to all. Pts in CR: A: Surgery+adj RIT IP B: Surgery RIT: monoclonal antibody HMFGI	St Ic—IV A: 25 pts B: 20 pts All pts in pathol. CR after CHT	Follow up median 59 m OS% A 80 B 50 p = 0.003	Significantly better OS for patients treated adjuvantly with RIT IP. Small material but well-matched controls. P3
Pickel 1999 (8) C	CHT vs. CHT+RT as adj treatment A: Surgery+CHT +WAR B: Surgery+CHT WAR: 30 Gy to whole abdomen+21.6 Gy to pelvis+12 Gy to para-aortic nodes	1985–1992 St Ic–IV A: 32 pts B: 32 pts	OS% DFS% at 5 y A 59 49 B 33 26 p = 0.029 p = 0.013	Significantly better OS and DFS with adjuvant CHT+ RT compared with CHT alone. Well-designed study but smallmaterial. C3
Sorbe 1999 (6) C	Value of adj treatment with CHT or RT Induction CHT to all, followed by A: Surgery+WAR B: Surgery+CHT C: Surgery WAR: 20 Gy/20 fr to whole abdomen+20 Gy/12 fr to lower abdomen and pelvis.	1988–1993 St III 98 pts in pathol. CR after induction CHT A: 32 pts B: 32 pts C: 34 pts	Follow up median 8 y OS% PFS% A 70 52 B 53 24 64 24 ns A vs. B p = 0.048 A vs. C p = 0.039 Group A: acute RT-related toxicity: intestinal 60%, bladder 12%. Late bowel reactions, grade 1 5.8%, grade 3 10.1% (4 bowel obstructions requiring surgery). No severe side effects in gr B or C.	In patients with complete pathological remission, significant difference in DFS between consolidation with RT or CHT vs. surgery alone. Small material. Well-conducted study. C3

Abbreviations: CHT = chemotherapy; DFS = disease-free survival; IP = intraperitoneal; ns = no significant; OS = overall survival; PFS = progression-free survival; pts = patient(s); m = month(s); RIT = radioimmunotherapy; RT = radiotherapy; WAR: whole abdominal radiation; CR = complete remission.
CHT Ref. (4): Melphalan or melphalan+doxorubicin, or melphalan+doxorubicin+cisplatin.
CHT Ref. (9): Carboplatin+epirubicin+prednimustine.
CHT Ref. (10): Epirubicin+cisplatin.

	1 = High	2 = Moderate	3 = Low	Total
C		1/257	5/509	6/766
P		1/45	1/45	
R		1/251	2/220	3/471
Total		2/508	8/774	10/1 282

CONCLUSIONS AND COMMENTS

There is a general consensus that adjuvant therapy is not needed in patients operated on for ovarian cancer stage Ia, grade 1 (Consensus NIH 1995).

– There is no scientific documentation supporting adjuvant radiotherapy for early-stage, low-risk patients ((3) C3).

Overview 3

Ovarian cancer. Other studies

Author Year (Ref. no.) Design	Aim/Study question	Patient population	Results			Conclusion/comments
Gelblum 1998 (12) R	Palliation with RT in Cp refractory tumours	1980–1995 St Iib–IV 47 pts	70% complete resolution of symptoms 24% partial resolution 2 unassessable Median duration of response 11 months			Irradiation may give palliation in cisplatin refractory ovarian cancer. R3
Kaldor 1995 (9) Case control study R	Secondary bladder tumors following different treatments. A: Cases with bladder tumour B: Matched controls	1960–1987 A: 63 pts B: 188 controls Treatments: RT CHT RT+CHT CHT: either cyclophosphamide or melphalan or thiotepa		RR Compared to surgery alone	95% CI	Highest risk for secondary bladder tumours after RT+CHT. CHT including cyclophosphamide sign. increased the risk, whether or not RT was given. The risk continues to increase more than 10 y after treatment. Well-conducted case-control study. R1
			RT	1.9	0.77–4.9	
			CHT	3.2	0.97–10	
			RT+CHT	5.2	1.6–16	

Abbreviations: CHT = chemotherapy; CI = confidence interval; Cp = cisplatin; DFS = disease-free survival; IP = intraperitoneal; ns = no significant; OS = overall survival; pts = patient(s); RIT = radioimmunotherapy; RR = relative risk; RT = radiotherapy.

No studies have been reported where adjuvant radiotherapy has been compared with no adjuvant therapy in early-stage, high-risk patients.

- Adjuvant radiotherapy, either whole abdominal irradiation or intraperitoneal P^{32}, has been compared with adjuvant chemotherapy in early-stage, high-risk patients. There is no scientific evidence to show that there is a difference in efficacy ((3) C3, (4) C2, (5) C3).
- There is some evidence that adjuvant radiotherapy after radical surgery leads to an increased disease-free survival for patients with advanced-stage ovarian cancer ((6) C3, (7) R3, (8) C3).
- There is little documentation on long-term side effects (second malignancy) after adjuvant radiotherapy and no conclusions can be drawn ((9) R1).

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