10. **Ovarian Cancer**

Introduction

In 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 65–69 years. The Nordic countries have the highest incidence of ovarian cancer in the world. According to the latest results from Cancer Registry of Sweden the 5-year survival rate for all stages was 36.5 per cent for women diagnosed 1964–66 and 44.6 per cent for women diagnosed 1993–96.

Histologically ovarian cancer is divided into many prognostically important subtypes.

Epithelial tumours represent the largest group, 95 per cent 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 of FIGO (International Federation for Gynecology and Obstetrics). Stages IA–IIA are considered to belong to the group of early tumours, as they are confined to the gynecological organs, the advanced stages IIB–III are spread outside gynecological organs as well as in abdomen and stage IV outside the abdominal cavity.

Tumour stage is of major importance in treatment and prognosis. Tumour symptoms are vague, hence ovarian cancer is often detected late. Approximately 2/3 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 50s, surgery and radiotherapy were the dominant treatment modalities. Since the introduction of chemotherapy during the late 50s and its demonstrated effect in advanced ovarian cancer, radiotherapy has lost its importance and has been more and more 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 the surgical treatment. Standard treatment of ovarian cancer today is primary debulking surgery with maximum reduction of tumour volume, which often is followed by intensive chemotherapy, expecially 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 involve 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 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
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**

Assessment of new literature

Search method and selections

Computerized literature searches were performed in Medline for 1994–October 2001. The MeSH search term ovarian neoplasms was used in combination with radiotherapy as a subheading, MeSH-term and textword. Limitations to the following study designs were made: randomized 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 Cochrane Library. As all the referees (Nina Einhorn, Claes Tropé, Mona Ridderheim, Karin Boman, Bengt Sorbe) are specialists in gynecological oncology and experts in all three gynecological tumour types decided by the SBU to be reviewed, a joint meeting of all referees was organised in Stockholm to select relevant abstracts and publications.

Initially 51 abstracts concerning ovarian cancer were received by the referees. Two more studies recently published were added, to a total of 53 abstracts. All abstracts as well as most of the publications were discussed by the referees and decision was made for further analysis of ten publications and description of one abstract with unpublished data. 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 materials
D	10	general topics not relevant to the aim of the study

Of ten analysed publications six represent randomized clinical trials. One abstract with unpublished data also represents a randomized trial [11].

Overview of new studies

Early stages (Ia-IIc) postoperative treatment

Overview 1 (after the list of references)

The literature shows that:

- The main treatment for patients with early stages of ovarian cancer (stage 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 to surgery plus adjuvant RT.
- 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 p32. When adjuvant chemotherapy was compared to 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

Overview 2 (after the list of references)

The literature shows that:

- All reported studies are small, with less than 100 pts (two studies) or less than 50 pts (three 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

Overview 3 (after the list of references)

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).

	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 for ovarian cancer stage Ia, grade 1 (Consensus NIH 1995).

- There is no scientific documentation supporting adjuvant radiotherapy for early stage low risk patients. ([1]C3).

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

- Adjuvant radiotherapy, either whole abdominal irradiation or intraperitoneal p32, has been compared to adjuvant chemotherapy in early stage high risk patients. There is no scientific evidence that there is a difference in efficacy. ([3]C2, [1]C3, [2]C3).
- There is some evidence that adjuvant radiotherapy after radical surgery leeds to an increased disease free survival for patients with advanced stage ovarian cancer. ([10]C3, [4]R3, [9]C3).
- There is a poor documentation on long term side effects (second malignancy) after adjuvant radiotherapy and no conclusions can be drawn. ([7]R1).

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Overview 1 *Ovarian cancer. Early stages (Ia-IIc), postoperative treatment*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Dent 2000 [3] C	Comparison between different adj treatments **A:** Surgery + WAR, 22.5 Gy/10 fr **B:** Surgery + adj CHT **C:** Surgery + p32 IP CHT = melphalan	1975–84 St Ia–IIa, IIb, IIIa A 107 pts B 106 pts C 44 pts (closed early due to toxicity)
Young 1999 [11] C	CHT vs isoptope RT as adj treatment **A:** Surgery + p32 IP **B:** Surgery + adj CHT CHT=cyclophosphamide + cisplatin	1986–94 St I–IIa high risk (grade 2, 3) A 98 pts B 107 pts
Bolis 1995 [1] 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	1983–90 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
Chiara 1994 [2] 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	1985–89 St I–II, grade 2, 3 A 36 pts B 34 pts

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

Results	Conclusion/Comments
follow-up median 13,5 y **OS% DFS%** A 45 50 B 49 62 C 50 ns 51 ns	Second malignancies: sign increase compared to age matched population. No sign difference between treatment groups. **C2**
follow-up median 5 y **DFS%** A 66 B 77 ns	No difference in DFS between groups. 2 pts with bowel perforation in gr A. **Abstract**
follow-up median 5 y **OS% DFS%** I. A 88 83 B 82 ns 65 p=0.06 II. A 81 85 B 79 ns 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**
OS% RFS% at 5 y A 71 74 B 53 ns 50 ns Diarrhoea (WHO gr 3–4) 28% in gr B. One late bowel obstruction in gr B.	No difference in OS or RFS between surgery + adjuvant CHT and surgery + adjuvant RT. Small material. L arge protocol violation for radiotherapy because of patient–doctor decision (44 pts treated with CHT and 25 with WAR). **C3**

Overview 2 *Ovarian cancer. Advanced stages – postoperative treatment*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Einhorn 1999 [4] 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 (1976–84) B 98 pts (1991–92)
Fyles 1998 [5] 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.	1981–90 St I–III A 67 pts B 58 pts
Nicholson 1998 [8] 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
Pickel 1999 [9] 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 paraaortic nodes.	1985–92 St Ic–IV A 32 pts B 32 pts
Sorbe 1999 [10] 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.	1988–93 St III 98 pts in pathol CR after induction CHT. A 32 pts B 32 pts C 34 pts

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
CHT ref [4.] Melphalan or melphalan + doxorubicin, or melphalan + doxorubicin + cisplatin
CHT ref [9.] Carboplatin + epirubicin + prednimustine
CHT ref [10.] Epirubicin + cisplatin

Results	Conclusion/Comments
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 of advanced ovarian cancer. New technique of RT with homogenous doses to almost whole abdomen. In 15% of patients interruption of treatment due to hematological toxicity. **R3**
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**
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**
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 small material. **C3**
follow-up median 8 y **OS%** **PFS%** A 70 52 B 53 24 C 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**

Overview 3 *Ovarian cancer. Other studies.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Gelblum 1998 [6] R	Palliation with RT in Cp refractory tumours	1980–95 St IIb–IV 47 pts
Kaldor 1995 [7] Case control study R	Secondary bladder tumours following different treatments. **A:** Cases with bladder tumour **B:** Matched controls	1960–87 A 63 pts B 188 controls Treatments: RT CHT RT + CHT CHT: either cyclo-phosphamide or melphalan or thiotepa

CHT: chemotherapy; C.I.: 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

Results	Conclusion/Comments
69.7% 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**
RR (Compared to surgery alone) / **95% C.I.** RT 1.9 / 0.77–4.9 CHT 3.2 / 0.97–10 RT + CHT 5.2 / 1.6–16	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**