

9. THE MANAGEMENT OF BORDERLINE OVARIAN TUMOURS

BACKGROUND

Borderline ovarian tumours are also known as atypically proliferating epithelial ovarian tumours or tumours of low malignant potential. They account for about 15% of all epithelial ovarian malignancies.¹ They tend to occur in young women and around 75% are stage 1 at time of diagnosis. Bilateral ovarian involvement is present in one quarter to one third of cases, sometimes only microscopically. Serous tumours are the most common epithelial type. Histologically, they are characterised by cellular stratification, cytological atypia and epithelial tufting, but without evidence of destructive stromal invasion.

Key point:

- Ovarian tumours of borderline ovarian tumours, account for about 15% of all epithelial ovarian malignancies. They tend to occur in young women and around 75% are stage I at time of diagnosis.

Most women with borderline tumours present with disease confined to the ovary. Whilst these women may be surgically upstaged, the presence of non-invasive metastatic deposits does not apparently affect the outcome, provided the metastatic component is an implant as opposed to showing signs of invasion. These non-invasive metastatic deposits should probably be considered multifocal disease field change.

SURVIVAL RATES FOR BORDERLINE TUMOURS

A recent meta-analysis² suggests that survival for stage I tumours is virtually 100%, whilst survival for advanced stage tumours with non-invasive implants is 95% and survival for tumours with invasive implants is 66%, after 7.4 years of follow-up. Microinvasion in the primary ovarian tumour was associated with a 100% survival rate at 6.7 years of follow-up. A recent publication based on the Surveillance, Epidemiology and End Results (SEER) Program, looking at relative survival in over 2800 women with low malignant potential (LMP) tumours, demonstrated a 10 year relative survival of 95%. The authors felt that the diagnosis of an ovarian tumour of LMP conveys a relatively benign prognosis and recommended that conservative surgery be considered in younger women with early-stage disease.³

MANAGEMENT OF BORDERLINE OVARIAN TUMOURS

FERTILITY CONSERVING SURGERY

Management of low grade borderline tumours is dependent upon the woman's wishes for fertility. Where the tumour is confined to the ovary and fertility sparing surgery is appropriate, either a unilateral salpingo-oophorectomy or ovarian cystectomy is appropriate, minimising trauma to the contralateral ovary by unnecessary biopsy. Bilateral ovarian cystectomy is equally acceptable if both ovaries are involved. Limited surgical staging should be performed to include resection of any peritoneal deposits and an omental biopsy (*see chapter 8 – Management of a pelvic mass*).

Care must be taken with interpretation of frozen section reporting, particularly of mucinous tumours, which must await routine paraffin sectioning to exclude invasive mucinous adenocarcinoma. Where doubt exists and fertility is still an issue, fertility sparing surgery is indicated. Where frozen section has reported a high grade borderline mucinous tumour it is probably prudent to stage those patients as though they were an early stage invasive ovarian carcinoma (*see chapter 5 – The biology and pathology of ovarian tumours*).

All mucinous tumours should have appendicectomy included as part of their procedure. There is a 15% chance of synchronous tumours, as mucinous tumour may be as a result of appendiceal seeding as with pseudomyxoma peritonei. Lymphadenectomy or diaphragmatic scrapings are of no value unless suspicious disease exists. Pelvic lymphadenectomy was reported by Leake⁴ as revealing metastatic disease in 21% of cases but whilst these patients had a statistically higher chance of recurrence, it did not influence their survival. There appears to be no case to restage patients who have been referred from outlying centres without appropriate surgery, rather surveillance is appropriate.⁵ Bell *et al.*⁶ also suggested that residual tumour at completion of surgery was a poor prognostic factor.

SURGERY WHERE CONSERVATION OF FERTILITY IS NOT REQUIRED

Where patients have completed their childbearing then a complete hysterectomy with bilateral salpingo-oophorectomy and omentectomy together with resection of any obvious disease is the treatment of choice. Resection should be limited to removal of all obvious disease and again no benefit exists for lymphadenectomy or random peritoneal or diaphragmatic biopsies.

ADJUVANT THERAPY

There is no role for adjuvant therapy for borderline tumours. Survival for stage I disease with surgery alone, in four consecutive randomised trials is so high (99%) that adjuvant therapy is unlikely to offer a survival advantage.⁷

The adjuvant therapy in the four trials consisted of:

1. External irradiation combined with intraperitoneal instillation of radioactive gold or external irradiation alone;
2. Intraperitoneal radioactive therapy followed by N, N', N'', triethylenethiophosphoramidate (thio-TEPA) or no further treatment;
3. thio-TEPA or no adjuvant therapy; and
4. cisplatin or ³²P (colloidal chromic phosphate) treatment.

In advanced stage I tumours no survival advantage has been demonstrated for adjuvant therapy. Kaern *et al.*⁸ reported on 370 patients, some of who received adjuvant therapy. Those without residual disease performed equally or better than those without adjuvant therapy.⁸

Guideline - Role of adjuvant therapy for Stage I borderline ovarian tumours	Level of Evidence	Refs
There is no role for adjuvant therapy for Stage I borderline ovarian tumours.	I	7

FOLLOW UP

Surveillance of patients with stage I borderline ovarian disease in 164 patients reported by Zanetta *et al.*⁹ suggested a recurrence rate of 17% (28/ 164), five of whom had invasive disease. The CA125 estimation was only elevated in 8 patients, and so they recommend three monthly transvaginal ultrasound for 2 years, and six monthly thereafter. Long term review is indicated as it is recognised that late recurrence is common with borderline tumours. They report that 161 women are alive without disease after 71 months. Interestingly in women with stage IB disease 5 of 14 (36%) recurred although all were salvaged with further surgery. They concluded that ultrasound and CA125 estimation were the best method of continuing surveillance.

The role for completion hysterectomy and oophorectomy following completion of childbearing is controversial, in the absence of recurrent disease. Should recurrence occur secondary cytoreduction is treatment of choice.

Key point:

- The role for completion hysterectomy and oophorectomy following completion of childbearing is controversial, in the absence of recurrent disease. Should recurrence occur, secondary cytoreduction is treatment of choice.

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10. SURGERY FOR INVASIVE OVARIAN CANCER

The surgical approach is the cornerstone of all management of ovarian cancers.

Surgery has a major role in the initial cytoreduction, for interval cytoreduction, and also in the management of persistent or recurrent disease.

PRIMARY CYTOREDUCTIVE SURGERY

Primary cytoreductive surgery is used as the initial management of women with ovarian cancer. It is employed to facilitate and confirm the diagnosis, as well as being definitive in removing the tumour(s) as part of the initial therapy. Primary cytoreduction typically includes total abdominal hysterectomy; bilateral salpingo-oophorectomy; omentectomy; and resection of metastatic lesions from the peritoneal surfaces or from the bowel. A number of retrospective studies of cytoreductive surgery have shown the favourable prognostic effect of minimal residual disease in terms of median survival duration.^{1,2,3,4}

Guideline - Primary cytoreduction	Level of Evidence	Refs
Primary cytoreduction is considered the initial treatment of choice for women with ovarian cancer and typically includes: <ul style="list-style-type: none">• total abdominal hysterectomy;• bilateral salpingo-oophorectomy;• omentectomy; and• resection of metastatic lesions from the peritoneal surfaces or from the bowel.	IV	1,2,3

Key point:

- Primary cytoreduction is considered the treatment of choice for most patients who are initially referred to Gynaecological Cancer Centres.

Optimal benefit results when all gross tumours can be excised safely.¹ A meta-analysis of 58 studies found that maximum cytoreductive surgery produced a small improvement in median survival time.⁵ This study was biased against surgery by the inclusion of a number of studies which did not use optimal chemotherapy, and by the variable definitions of 'optimal' cytoreduction (*see chapter 11 – Chemotherapy*).

Key points:

Cytoreductive surgery is considered to offer three theoretical advantages:

- Removal of bulky tumour masses may improve the physiological status of the patient by alleviating the nausea and early satiety often associated with a large omental mass, improving bowel function, and decreasing the volume of ascites.
- Cytoreduction may eliminate the hypoxic areas of a tumour, thereby improving the perfusion of the residual tumour nodules, and increasing the growth fraction of the tumour. (Well perfused, actively divided cells are more likely to respond to chemotherapy or radiotherapy).⁶
- Resection of bulky disease enhances the immunological competence of the patient.

Primary cytoreduction typically includes resection of metastatic lesions from the peritoneal surfaces or from the bowel. The latter may necessitate bowel resection, so preoperative bowel preparation is necessary in all patients. Primary reanastomosis is always feasible following small bowel resections, and usually feasible following colonic resection.

Bulky pelvic or para-aortic lymph nodes should be resected if possible but whether or not there is benefit from systematic lymphadenectomy is being tested currently in an international randomised trial.⁷

The goal of cytoreduction should be to remove all macroscopic disease, but as this is seldom feasible, as much disease as possible should be removed. Optimal cytoreduction is usually defined as residual disease ≤ 2 cm. When performed by gynaecological oncologists, optimal cytoreduction can be achieved in 70-90% of patients^{2,8}, whereas resection of all macroscopic disease is feasible in only about 12% of cases. In those women for whom resection of all macroscopic disease is feasible, the 5-year survival rate is around 50%.⁹

Epithelial ovarian cancer is a tumour of intermediate chemosensitivity, with response rates to first line chemotherapy in the order of 70%. A meta-analysis of 38 chemotherapy studies reported that residual disease of ≤ 2 cm ($P = 0.011$) and the use of platinum chemotherapy, ($p=0.005$) were the only independent prognostic factors in multivariate analysis¹⁰ (*see chapter 11 – Chemotherapy*).

Morbidity from cytoreductive surgery is generally well tolerated. In a study of 472 primary cytoreductive operations for ovarian cancer from Helsinki, intraoperative bleeding in excess of 1000 ml occurred in 21% of cases. In addition, 18% of women had urinary tract infections, 7% had bowel complications (mainly prolonged ileus), 4% had fever, 3% had wound complications, and 2% developed thromboembolism. Only five women (1%) died post-operatively.¹¹

INTERVAL CYTOREDUCTIVE SURGERY

Interval cytoreductive surgery is defined as surgery undertaken after a period of neoadjuvant chemotherapy, which is given either because optimal primary cytoreduction (residual disease of ≤ 2 cm) was not achieved, or because the woman's general medical condition was too poor initially to undergo surgery.

If cytoreductive surgery is to be performed it should be undertaken by a specialist gynaecological oncologist in a specialist centre (*see chapter 6 – Multidisciplinary management of women with ovarian cancer*).

Definitions of sub-optimal cytoreduction have varied within the literature, reflecting the difficulty of accurately describing residual tumour burden within the various peritoneal sites and lack of agreement on the amount of residual tumour that constitutes optimal cytoreduction.¹² Conventionally, women with tumour nodules of greater than 2 cm diameter at the completion of cytoreductive surgery are regarded as suboptimally cytoreduced.

There has only been one major prospective randomised trial of interval cytoreductive surgery. It was conducted by the European Organisation for Research and Treatment of Cancer (EORTC), and was a study of interval cytoreduction following three cycles of chemotherapy for women who had a suboptimal primary operation, defined in this study as tumour deposits greater than 1 cm remaining.¹³ Women whose tumour progressed on the three cycles of treatment were ineligible. There were 319 patients randomised, and both progression-free and overall survival were longer in the group having interval cytoreduction ($p = 0.01$). Although this is the only randomised prospective study of cytoreduction, it does not imply that all patients should have initial definitive surgery delayed until chemotherapy has been given.

Elective interval cytoreduction following neoadjuvant chemotherapy may also be indicated if the woman's general medical condition is poor, particularly in the presence of massive ascites and a large pleural effusion.

Randomised studies in this setting have not been conducted, but the use of neoadjuvant chemotherapy in selected cases has demonstrated comparable survival to patients treated with conventional cytoreductive surgery followed by chemotherapy.¹⁴ In the latter setting, a diagnosis of malignancy should be established cytologically prior to the initiation of chemotherapy. (*For management of borderline ovarian tumours, see chapter 9*).

Guideline - Interval cytoreduction	Level of Evidence	Refs
Neoadjuvant chemotherapy and interval cytoreduction may be considered if optimal primary cytoreduction was not achieved.	II	13

SECONDARY CYTOREDUCTIVE SURGERY

SURGERY FOR PERSISTENT OR RECURRENT DISEASE

Patients who develop progressive disease on chemotherapy have a very poor prognosis. Surgery in this context offers no survival advantage and should be limited to symptomatic care, for example, for the relief of an acute bowel obstruction (*see chapter 16 – Palliative care*).

Secondary cytoreductive surgery is confined to surgery undertaken to further debulk the cancer in women who have persistent disease, following a completed course of chemotherapy, or who subsequently experience biochemical and/or clinical relapse.

The outcomes for patients who have persistent disease at the end of the primary treatment and who then undergo surgery are poorer than for those who have a good initial surgically documented response to their chemotherapy and then later relapse. The longer the interval from complete remission to evidence of relapse, the more likely there will be a substantial benefit from a second attempt at surgery^{15,16,17,18,19,20,21} (*see chapter 11 – Chemotherapy*).

Guideline - Surgery in women who develop progressive disease during initial chemotherapy	Level of Evidence	Refs
Surgery has no place for women who develop progressive disease during their initial chemotherapy program.	IV	15, 16

A recent study by Tay *et al.*²² reviewed 336 patients treated by gynaecological oncologists between 1996 and 1998. Forty six patients underwent secondary cytoreductive surgery after a disease free interval. The authors report that in those women in whom all remaining disease could be cleared, and those who had a disease-free interval of at least 24 months after initial treatment, survival could be significantly prolonged.

Key points:

Secondary cytoreductive surgery may benefit women with^{23,24}:

- Long disease-free interval (especially >2 years)
- Younger age
- Good performance status
- Isolated recurrences, especially in the pelvis, if resection can be completed

In contradistinction to the situation in colon cancer, there are no data to substantiate the use of liver resection for recurrent disease. The most common clinical situation which women with ovarian cancer experience is disease in the upper abdomen,

usually involving the diaphragms and the liver parenchyma. This is equally difficult to manage surgically in the primary and recurrent disease. CT scanning and abdominal and transvaginal imaging studies are therefore mandatory prior to deciding on such surgery.

Data on the rate of success of attempted secondary debulking surgery are few. Most women who undergo such procedures opt for cytotoxic therapy following surgery although some have been reported to have a satisfactory response without postoperative therapy.²⁵ Therefore, the effect of the surgery itself is unclear.

Key point:

- A randomised trial is required to compare surgery plus chemotherapy, with chemotherapy alone, in disease which has relapsed more than 24 months since discontinuation of primary treatment.

SECOND-LOOK SURGERY

'Second-look' operations have been traditionally undertaken following the completion of the initial treatment program, which has usually involved a primary laparotomy, followed by six cycles of combination chemotherapy. The accuracy of laparoscopy and laparotomy in detection of disease seems comparable.^{26,27,28} Although it is clear that second-look surgery does provide reliable prognostic information,²⁹ it remains controversial whether such procedures improve survival.^{30,31,32,25,33} Although the data are conflicting, there are a number of publications, particularly about platinum-treated patients, suggesting a survival advantage 'when macroscopic residual disease can be reduced to microscopic'. The introduction of taxanes and other agents as possible second line treatment should stimulate the question to be revisited. A recent randomised controlled trial comparing WART, chemotherapy and no further treatment for advanced ovarian cancer (*see FIGO Staging, Introduction- p3*) in women with complete surgical and pathologic remission after induction chemotherapy, showed a survival advantage for WART,³⁴ although the numbers did not reach statistical significance (*see chapter 12 – Radiation Therapy*).

Key point:

- Second-look procedures should only be undertaken in the context of a research setting, to investigate further treatment such as chemotherapy or Whole Abdominal Radiation Therapy (WART).

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II. CHEMOTHERAPY

Surgical staging is the cornerstone to all subsequent treatment discussions in ovarian cancer. The careful and accurate surgical procedure will determine the true stage, and this must be performed meticulously (*see Introduction, chapter 10 – Surgery for invasive ovarian cancer and Appendix 4 - Gynaecological oncology training requirements*).

This is especially important for early stage disease, as stages IA and IB may not always require adjuvant chemotherapy, and one must be as certain as is possible, that there is no tumour in the ‘sanctuary’ or hidden sites, especially omentum, diaphragms and lymph nodes.

Outcomes of treatment are best for women managed in a multidisciplinary care setting, with medical, nursing and allied health staff specially trained in the management of patients with ovarian cancer (*see chapter 6 – Multidisciplinary management of women with ovarian cancer*). Wherever possible, chemotherapeutic management of patients with ovarian cancer should be undertaken in conjunction with a major referral centre for the management of gynaecological malignancy.

Key points:

- Surgical staging is the cornerstone to all subsequent treatment discussions in ovarian cancer.
- Wherever possible chemotherapeutic management of patients with ovarian cancer should be undertaken in conjunction with a major referral centre for the management of gynaecologic malignancy.

WHICH PATIENTS WITH EARLY OVARIAN CANCER SHOULD RECEIVE CHEMOTHERAPY?

Provided that surgical staging is meticulous and follows all the guidelines, not all women with early stage ovarian cancer will benefit from chemotherapy.¹ If surgery is not optimal, chemotherapy can reduce the risk of recurrence and death in early ovarian cancer. The absolute benefit for an individual patient will vary according to their risk of relapse, which is closely related to their disease stage.^{1,2,3,4}

Patients with borderline tumours, even with documented metastases, have an excellent prognosis (*see chapter 5 – The biology and pathology of ovarian tumours, and chapter 9 – The management of borderline ovarian tumours*). In the absence of documented invasive implants, adjuvant chemotherapy is not indicated.⁵

Guideline - Adjuvant chemotherapy for women with early stage ovarian cancer	Level of Evidence	Refs
Adjuvant chemotherapy with a platinum agent is recommended for patients with high grade or clear cell histology because they are known to have a higher relapse rate.	II	1
Patients with stage IA or IB well or moderately differentiated tumours do not require adjuvant chemotherapy because their risk of relapse is low, and the toxicity not justified.	II	2
Adjuvant chemotherapy is not indicated in patients with borderline tumours (unless invasive implants are confirmed histologically).	II	3

ADJUVANT TREATMENT OF EARLY OVARIAN CANCER

Two recently reported randomised trials examined the effect of immediate chemotherapy after surgical resection of early ovarian cancer compared to a policy of delaying such treatment until clinically indicated by the development of symptoms. The ICON1 trial⁶ randomised 477 patients with histologically confirmed epithelial ovarian cancer on the pragmatic basis that the treating clinician was uncertain of the need for immediate adjuvant chemotherapy. Surgically, all visible tumour had to have been removed. Various platinum-based chemotherapy regimens were allowed. A parallel study¹ included 448 patients with a variety of FIGO stages after various degrees of surgical staging. Again the randomisation was between immediate and delayed chemotherapy, and chemotherapy had to consist of at least four courses (six were recommended) of a platinum-based chemotherapy.

Although results of the two trials have been presented separately, a prospectively designed combined analysis⁷ was also reported. Immediate chemotherapy compared to no (delayed) chemotherapy resulted in improved 5-year overall survival (82% vs. 74%; HR= 0.67, C.I 0.50 to 0.90; p=.008) and improved 5-year recurrence-free survival (76% vs. 65%; HR = 0.64, C.I 0.50 to 0.82, p= 0.001). In the combined analysis, the survival benefit was limited to those with non-optimal staging, suggesting that patients more at risk of unappreciated residual disease are more likely to benefit from chemotherapy.

Guideline - The effect of platinum based adjuvant chemotherapy on women with early stage ovarian cancer	Level of Evidence	Refs
Platinum-based adjuvant chemotherapy improves recurrence-free and overall survival in women with surgically resected early ovarian cancer, who are at high risk of relapse.	II	6, 7

FIRST LINE TREATMENT OF ADVANCED DISEASE

Two individual-patient-data meta-analyses and seven additional randomised trials investigated the survival benefits of various options for first-line systemic chemotherapy for advanced ovarian cancer. A meta-analysis based on these nine studies indicated that,

when compared to non-platinum-based regimens, platinum, alone or in combination with other agents, improves survival when used as a first-line treatment, with a Mortality Hazard Ratio (HR) of 0.88; 95% C.I 0.79 to 0.98; p=0.02; n=1704). This translates into an absolute improvement of approximately 5% in the survival rate at two years (35% without platinum versus 40% with platinum).⁸

Another meta-analysis⁹ has supported the use of a platinum compound as the standard chemotherapy for ovarian carcinoma.

Guideline - First line treatment of advanced ovarian cancer	Level of Evidence	Refs
The first line treatment of advanced ovarian cancer ideally should include a platinum compound.	I	9

CISPLATIN OR CARBOPLATIN

A meta-analysis was published in 1998,⁹ containing twelve trials of carboplatin versus cisplatin with 2219 patients. The trialists concluded that there was no evidence of any difference between cisplatin and carboplatin when given as a single agent or in combination. There was no evidence that any group of women (by age, stage, progression-free survival (PS), residual tumour bulk, histology or grade) would do better with cisplatin versus carboplatin.

Subsequent randomised trials of the combination of carboplatin and paclitaxel have been performed since the publication of this meta-analysis.^{10,11,12} The consistent findings are that there is no significant difference in progression free or overall survival when carboplatin is substituted for cisplatin. Given the favourable toxicity profile and ease of administration yet equivalent efficacy of carboplatin this agent has become generally accepted as the preferred first line treatment.

Key points:

- Carboplatin is well tolerated by the great majority of patients, and in trained hands can be given safely even in relatively frail and/or elderly patients.
- In patients who decline intravenous chemotherapy, or are otherwise unsuitable for carboplatin, oral alkylating agent therapy (eg chlorambucil or melphalan) is a reasonable alternative treatment.

SINGLE AGENT PLATINUM VS. PLATINUM PLUS OTHER DRUGS

Despite the recent publication of a number of large, well conducted randomised prospective trials, this issue has not been completely resolved.

A meta-analysis¹³ performed before the introduction of taxanes used individual patient data from 1095 patients in a total of nine randomised trials of single agent platinum

versus platinum containing combinations. Although the Hazard Ratio of 0.91 (95% C.I 0.80 to 1.05; $p=0.21$) slightly favoured combination treatment, this result was not statistically significant.

The International Collaborative Ovarian Neoplasm (ICON) 2 trial¹⁴ compared carboplatin (AUC=5) to cisplatin (50 mg/m²) + cyclophosphamide + doxorubicin. The median survival was 33 months and 2 year survival 60% in both arms (mortality HR, 1.0; 95% C.I 0.86 to 1.16; $p=0.98$).

The International Collaborative Ovarian Neoplasm (ICON) 3 trial¹⁵ included a comparison of single agent carboplatin (AUC = 5-6) with carboplatin (AUC = 5-6) and paclitaxel (175 mg/m² over 3 hours) in 1421 patients. The median overall survival was not significantly different in the two arms, Hazard Ratio 0.98 (95% C.I 0.85 to 1.12, $p=0.73$).

Some authorities have criticised the design of the ICON studies, suggesting that there is a potential for unrecognised biases in these trials. Others believe that their sheer size makes the results quite robust. Despite the ICON results, the global standard remains treatment with combination chemotherapy. Ongoing trials are testing the addition of new drugs such as gemcitabine and topotecan to the combination of carboplatin and paclitaxel. There are no single agent control arms in any of the currently ongoing randomised controlled trials.

WHICH COMBINATION?

In early studies, the addition of doxorubicin to platinum and cyclophosphamide was shown to be beneficial in terms of overall survival.^{16,17-19} This survival benefit is small and was only detected from pooled data, so that its clinical utility has been questioned.¹⁹

ROLE OF PACLITAXEL

Two large randomised trials have compared cisplatin plus cyclophosphamide versus cisplatin-paclitaxel. These studies demonstrate a statistically significant survival advantage for the combination of cisplatin and paclitaxel over cisplatin and cyclophosphamide.^{20,21}

WHICH PLATINUM WITH PACLITAXEL?

A number of other studies investigated the preferable platinum analogue and duration of infusion of paclitaxel. Regimens employing carboplatin produce overall survival results apparently equivalent to those employing cisplatin, but with significantly less toxicity. Regimens incorporating a three hour infusion are as effective as longer infusions and more acceptable to patients.^{22,23} Taken together these studies support the combination of carboplatin and paclitaxel as standard of care for first line therapy of epithelial ovarian cancer.

Guideline - Current practice for first line chemotherapy	Level of Evidence	Refs
It is currently recommended that standard first line chemotherapy should be a combination of carboplatin (AUC x 6) and paclitaxel (175 mg/m ²) given every three weeks.	II	10, 12

The use of platinum and paclitaxel is supported by the results from two randomised controlled trials (RCTs), Gynecologic Oncology Group (GOG) 111²⁰ and OV10²¹. A third trial, GOG 132, is essentially a trial of concurrent platinum/paclitaxel chemotherapy versus sequential platinum/paclitaxel chemotherapy.²⁴ No significant survival advantage was observed for the combination arm. However, the conclusions which might be drawn from this study are uncertain since many patients eventually received both drugs.

ICON 3, a trial of either carboplatin alone or CAP vs carboplatin/paclitaxel in over 2000 women, does not support the addition of paclitaxel to carboplatin. The difference in results from trials such as GOG111 and OV10 may be explained by the lower dose of platinum providing an inadequate control arm. A pooled analysis has been conducted in an attempt to explain trial heterogeneity.²⁵

Criticisms of ICON 3 include the difference seen in results from large and small treatment centres and the lack of audit in the UK Medical Research Council (MRC) trials. It is however the largest study of chemotherapy in ovarian cancer ever completed.

The apparently comparable results of combination therapy versus single agent carboplatin suggest that when patients are either unsuitable for combination therapy on the basis of their concurrent medical conditions or their poor performance status, or are unwilling to accept the toxicity of combination therapy, that single agent carboplatin is an acceptable alternative treatment regimen. Given the favourable toxicity profile of carboplatin as a single agent, there are very few patients who would not tolerate this treatment.

Guideline - Single agent carboplatin	Level of Evidence	Refs
In patients unsuitable for combination therapy (on the basis of either concurrent medical conditions, performance status or by patient preference) single agent carboplatin is an effective and acceptable treatment for advanced ovarian cancer.	II	14

NEWER AGENTS AND CURRENT RESEARCH

Current research strategies include substitution of taxotere for paclitaxel, addition of a third drug (eg gemcitabine, topotecan) in combinations or sequential patterns, or longer durations of therapy. Data from the randomised trial of docetaxel/carboplatin (DC) versus paclitaxel/carboplatin (PC) have only been reported in abstract form but early survival data suggest that docetaxel is an alternative to paclitaxel and produces a different toxicity profile.

Ongoing studies GOG182/ICON5 are comparing the addition of new agents to the standard of carboplatin and paclitaxel (gemcitabine, topotecan and pegylated liposomal doxorubicin) either concurrently or sequentially. All patients in this trial will receive at 8 cycles of chemotherapy.

WHEN TO COMMENCE CHEMOTHERAPY?

Chemotherapy does not delay the healing of uncomplicated wounds. There would appear to be no advantage and potential disadvantage to delay chemotherapy longer than is required to allow reasonable recovery after surgery. Chemotherapy should commence as soon as practical after bowel function has recovered following surgery, ideally within two weeks of surgery.

SPECIAL CHEMOTHERAPY STRATEGIES:

INTRAPERITONEAL THERAPY

Intraperitoneal (IP) therapy has been advocated because of a putative advantage derived from the high intraperitoneal drug concentrations achieved. One large randomised prospective trial²⁶ reported a survival advantage for IP cisplatin over systemic cisplatin (both used in combination with intravenous cyclophosphamide). A second study found no superiority for intraperitoneal over intravenous administration.²⁷ Median survival was 49 months versus 41 months ($p < 0.02$) with the same survival benefits for micro and various sizes of macro residual disease.

A subsequent study has reported small survival gains associated with intraperitoneal chemotherapy.²⁸ Survival difference was of borderline statistical significance (RR 0.89) for intraperitoneal versus intravenous administration with a Relative Risk of 0.78 survival advantage improvement in progression-free survival, compared with intravenous administration. This study also confirmed the relative safety of administering cisplatin to patients with small volume residual advanced ovarian cancer outside the clinical research setting.²⁸ Both of these studies were conducted in patients with stage III disease with minimal residual disease.

Although intraperitoneal chemotherapy has its advocates in particular centres, given the complexity of the technique and the conflicting data, this treatment has not yet been accepted as a standard of care.

Although not standard of care, its use may be considered on an individual patient basis in a designated cancer centre. The optimal drug and dose for intraperitoneal therapy have not yet been determined in this setting.

Guideline - Intraperitoneal chemotherapy	Level of Evidence	Refs
Although intraperitoneal chemotherapy is not recommended as standard therapy its use may be considered on an individual patient basis at a designated cancer centre.	II	27

DOSE INTENSE OR DOSE DENSE STRATEGIES:

Dose intensity was suggested as a strategy to improve the effectiveness of chemotherapy by Levin and Hryniuk based on retrospective studies. The question has now been addressed in a number of prospective studies.

A phase III of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian cancer showed superior progression free survival for patients randomised to the experimental treatment arm and borderline improvement in overall survival.

The West of Scotland trials group³⁰ studied patients (stage IC to IV) receiving either cisplatin 100 mg/m² plus cyclophosphamide 750 mg/m² High Dose (HD) or cisplatin 50 mg/m² plus cyclophosphamide 750 mg/m². There was thus a two-fold difference in the planned dose and total dose. A planned interim analysis (at n=165) showed a significant survival advantage for the HD arm (median survival 114 v 69 weeks, P=0.0008) and the trial was closed. Longer follow up to median observation of 57 months however shows a much reduced survival benefit, with the difference in favour of the HD arm being seen almost exclusively in the first year of follow up. Importantly, long term neurotoxicity is much more a problem in the HD arm. Interestingly the authors chose to recommend a dose of 75 mg/m² of cisplatin as optimal, and yet this dose was not formally tested.

The GOG31 performed a randomised trial in 458 suboptimally debulked patients with > 1 cm residual stage III and IV. The arms were 4 courses of dose intensified (HD) CisDDP 100 mg/m² plus cyclophosphamide 1000 mg/m² q 3 weekly for four cycles, and CisDDP 50 mg/m² plus cyclophosphamide 500 mg/m² for 8 cycles. The study achieved a doubling of dose intensity without a difference in the delivered total dose, as designed. No significant difference in response rate or median survival was seen.

Two other large studies^{32,33} have increased both dose intensity and total dose, demonstrating greater toxicity in the HD arm, but no response or survival advantage.

Most authorities recommend standard dose intensity for cisplatin of 25 mg/m²/week, as used in the classic GOG studies.

Key point:

- Most authorities recommend standard dose intensity for cisplatin of 25 mg/m²/week, for advanced ovarian cancer, as used in the classic GOG studies.

HIGH DOSE CHEMOTHERAPY WITH STEM CELL SUPPORT

The previous discussion refers to increased dose intensity/ total dose which can be achieved with standard chemotherapy without growth factor support. Apart from intraperitoneal therapy, the other option is very high dose therapy.

There are large numbers of Phase I and II trials reporting ‘feasibility’ of very high (i.e. 8 to 10 fold increase) in dose/intensity. High response rates are described, but a major issue is that the patient cohorts are usually poorly described in terms of their disease being likely to still be platinum sensitive or resistant. Until results from randomised trials underway to evaluate High Dose (HD) chemotherapy – as part of initial therapy or as consolidation therapy after initial response to therapy – and to compare HD with standard dose chemotherapy are reported, HD therapy remains limited to the clinical trial setting.³⁴

Guideline - High dose therapy	Level of Evidence	Refs
The use of chemotherapy protocols utilising high dose therapy should only be offered as part of an appropriately designed clinical trial.	IV	34

MONITORING DURING CHEMOTHERAPY

During chemotherapy tumour response is assessed by clinical measurement of evaluable tumour (when present). Serum CA125 level is an important marker of response (or otherwise) to treatment. A confirmed rise of serum CA125 level to more than twice the upper limit of normal during follow up after first line chemotherapy accurately predicts tumour relapse.³⁵ CA125 has a serum half-life of approximately 6 days. During the first few (probably 3) cycles of treatment, the CA125 level reflects the effects of debulking surgery as well as chemotherapy, so that a fall in CA125 cannot be taken as definite evidence of tumour response. However, if CA125 is falling, treatment should continue to six cycles.

HOW LONG SHOULD FIRST LINE CHEMOTHERAPY CONTINUE?

Three randomised trials have addressed this issue for intravenous chemotherapy.³⁶⁻³⁸

Overall none of the studies reported a difference in the rate of complete pathological response (CR) or median survival. Therefore, it is concluded that treatment beyond six cycles cannot be recommended. In practice, occasional patients show a slow but continued response to chemotherapy (manifest by a continuing drop in CA125) and require more than six cycles to achieve complete response. In these unusual cases, it is recommended to continue treatment until CR is achieved, as long as toxicity is acceptable.

Key point:

- While treatment beyond six cycles cannot be recommended, in unusual cases where there is slow but continued response to chemotherapy (manifest by a continuing drop in CA125) treatment can continue until complete pathological response is achieved, as long as toxicity is acceptable.

CONSOLIDATION TREATMENT

This approach addresses a different concept, i.e. does further chemotherapy after achieving a response to initial treatment confer a benefit. The available evidence is limited, but includes studies by the North Thames Group³⁸ and the Swedish-Norwegian Ovarian Cancer group.³⁹ At present, the evidence does not support the use of maintenance or consolidation therapy, outside the context of a properly designed clinical trial.

Guideline - Maintenance or consolidation chemotherapy	Level of Evidence	Refs
The use of maintenance or consolidation chemotherapy should only be offered as part of an appropriately designed clinical trial.	II	38,39

RELAPSED DISEASE

Patients with relapsed disease are incurable, but many such patients may still derive useful responses from further therapy. It is important to recognise the heterogeneity of this patient population, both in terms of patient's wishes and goals, and also in likelihood of response to further therapy.

There is evidence that the interval between the end of first-line therapy and relapse (the treatment-free interval) is an important predictor of likelihood of response. The longer the treatment-free interval, the higher the likelihood of worthwhile response.^{40,41} However (with the rare exception of patients whose disease progresses during primary platinum-based therapy), there is no absolute disease-free interval which can be arbitrarily used to exclude a response to carboplatin.

Patients who do not respond to initial therapy, or who progress during initial chemotherapy, are considered platinum refractory, and an argument can be made for not considering further treatment.

In contrast, the potential importance of retreating with carboplatin in women *who have responded* to platinum during first line therapy should be stressed. Clinical experience demonstrates that a significant number of patients derive worthwhile benefit from re-treatment with carboplatin (even with a platinum-free interval of less than 12 months). Worthwhile response is uncommon, but not unknown, in women with a disease-free interval of less than six months.

Given its ease of administration and low toxicity, the principle of therapy for relapsed disease should be that the potential utility of single agent carboplatin should be exhausted before moving on to other agents.

Guideline - Treatment of relapsing disease	Level of Evidence	Refs
Patients relapsing more than six months after a confirmed response to initial treatment with platinum compounds should be considered for re-treatment.	IV	40, 41

Response to such treatment must be carefully monitored however, and treatment is only continued past two or three courses if there is evidence of response and improvement in symptoms.

It is important not to be misled by a fall in CA125 levels after aspiration of pleural effusions or ascites.

THE TREATMENT OF OVARIAN CARCINOMA NO LONGER SENSITIVE TO PLATINUM

Topotecan and pegylated liposomal doxorubicin are cytotoxics with some efficacy in terms of response rate and survival times in platinum/taxane resistant disease.^{12,42,43} Topotecan is associated with more haematological toxicity and requirement for dosage modification. Liposomal doxorubicin commonly causes mucositis and may cause plantar-palmar erythrodysesthesia but only requires a four-weekly dosing.

Tamoxifen has limited but definite activity in otherwise drug-resistant disease. Given its low toxicity profile, it should be considered where chemotherapy is inappropriate.

Key point:

- In patients with relapsed ovarian cancer, quality of life must be a major component of assessment.

It is important to note that it is well recognised that occasional patients can have multiple responses to treatment, and a relatively protracted survival. These patients typically have a long treatment free interval. In patients in whom the treatment free interval is relatively prolonged (e.g. 18 months or more) consideration should be given to further debulking surgery.

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12. RADIATION THERAPY

The initial management of ovarian cancer is surgical, but most patients will require further treatment with chemotherapy, radiotherapy or both, because of the high risk of intra-abdominal recurrence. Systematic study of the role of radiation therapy in the management of ovarian cancer has been limited by poor accrual to large randomised trials in this area, by pre-existing prejudices regarding the outcomes of such studies, and by concerns about the toxicity of abdominal radiation therapy.

ADJUVANT RADIOTHERAPY

In a small number of treatment series, post-operative adjuvant treatment with Whole Abdominal Radiation Therapy (WART) appears to have achieved a cure in approximately 75% of suitably selected patients.¹

COMPARISON BETWEEN WHOLE ABDOMINAL RADIOTHERAPY AND ADJUVANT CHEMOTHERAPY

No well-designed prospective randomised clinical study has ever been completed to compare the efficacy and toxicity of Whole Abdominal Radiation Therapy (WART) alone versus chemotherapy alone as an adjuvant therapy. It is therefore not possible to provide evidence to support evidence-based guidelines that categorically demarcate the choice between radiotherapy and chemotherapy. The appropriate use of one or both of these treatments should be carefully considered in the multidisciplinary management of women with ovarian cancer.

The role of WART as adjuvant treatment is still an open subject deserving further study. Cardenes and Randall have written a useful review on current issues and future directions.²

EFFICACY OF WART

Patients most likely to benefit from post operative WART are those who have received optimal cytoreductive surgery, and are classified as 'intermediate risk' according to the criteria used at Princess Margaret Hospital (PMH) in Toronto.³ This classification which uses stage, grade and residuum of tumour as prognostic factors, (Figure 12), has been validated internationally.⁴⁻⁶

Figure 12 Prognostic Subgroupings According to Stage, Residuum and Grade in Patients with Stages I – III

Stage	Residuum	Grade 1	Grade2	Grade3
I	0	Low risk		
II	0		Intermediate risk	
II	< 2cm			
III	0		High risk	
III	< 2cm			

WART is indicated as primary post-operative therapy in patients with stage I, II and III disease having no macroscopic disease in the upper abdomen and small macroscopic (0-2cm) residual disease in the pelvis.

Low-risk patients with stage I disease completely resected, with well differentiated non adherent tumours and negative peritoneal cytology, are cured by operation alone in approximately 95% of cases, and do not require post-operative therapy.

Conversely, WART is inadequate treatment in the PMH 'high risk' category women, in whom only 20% remain free of disease at 10 years after WART alone. It has been known for many years that there is a relationship between tumour control probability, radiotherapy dose, and volume of disease for tumours of various histologies.⁷

For ovarian cancer the estimated relationship between tumour size and dose required to achieve any reasonable chance of tumour eradication (the 'cancericidal dose') is shown in Table 4.⁸

Table 4 Estimated relationship between tumour size and dose of radiation required to achieve reasonable chance of tumour eradication

Tumour Size	Cancericidal Dose
2cm	50 – 60Gy
0.5 – 2.0cm	45 – 50Gy
Microscopic	25 – 30Gy

ADJUVANT CHEMOTHERAPY FOLLOWED BY WART

The role of sequential chemotherapy followed by WART has been studied in two small prospective randomised studies.^{9,10} The available data suggest that WART is at least as effective as continued chemotherapy for women with advanced ovarian cancer and that long term survival may occur where consolidation WART is used for patients with negative second look laparotomy following chemotherapy.¹¹

A recent randomised controlled trial comparing WART, chemotherapy and no further treatment for advanced (FIGO stage III) ovarian cancer, showed a survival advantage for WART in women with complete surgical and pathologic remission after induction chemotherapy, although the difference did not reach statistical significance.¹² This lack of statistical significance may be explained by the small sample size and the survival advantage may be clinically important. It should also be noted that between-group difference at baseline in tumour grade (one of the prognostic factors for ovarian cancer) could explain some of the differences in the results. The proportion of women with well or moderately well differentiated tumours in the chemotherapy group was 26%, compared to 50% and 42% in the radiotherapy and control group respectively.

Guideline - WART for stage III patients	Level of Evidence	Refs
Whole Abdominal Radiation Therapy (WART) should be considered in stage III ovarian cancer patients with complete surgical and pathologic remission at second-look laparotomy.	II	12

COMPLICATIONS OF WART

There are limits to the radiation tolerance of normal organs included in the WART target volume, particularly in the upper abdomen.⁸ The complications of WART are acceptable as long as an open field technique is used, radiotherapy doses are limited to 45-50Gy in 1.8-2.0Gy fractions in the pelvis, and 22.5-27.5Gy in 1.0-1.2Gy fractions in the upper abdomen, and the dose to the kidneys is limited to < 20Gy by appropriate shielding.¹³ The radiotherapy protocol as set out by PMH Toronto is well tried and gives acceptable toxicity.^{3,8} Analysis of complications in 600 patients treated at PMH Toronto showed that most patients experience temporary acute side effects during WART, including

nausea, vomiting and diarrhoea. Myelosuppression was a common reason for treatment interruptions, and resulted in 10% of patients failing to complete WART.

The late complications of WART included chronic diarrhoea in 14% of patients, transient hepatic enzyme elevation (44%), symptomatic basal pneumonitis (4%), cystitis (2.8%) and bowel obstruction (4.2%), treated conservatively (1.5%) or with surgery (2.7%).

PMH Toronto conducted a randomised study of two doses of WART, which compared 22.5Gy in 22 fractions versus 27.5Gy in 27 fractions. A pelvic boost of 22.5Gy was used in both arms.¹⁴ The study involved 125 patients and concluded there was no difference in survival, tumour control or toxicity between the higher dose and lower dose of WART. Serious bowel toxicity was seen in three patients: two in the low dose and one in the high dose arm.

PALLIATIVE RADIOTHERAPY

Three studies have demonstrated the effectiveness of radiotherapy in the palliative treatment of brain metastases, vaginal bleeding, rectal bleeding, pelvic pain and other symptoms.

One study by Corn *et al.*¹⁵ evaluated 4027 women with ovarian cancer over a 30 year-period. Of these 32 were found to have cerebral metastases and each received fractionated whole-brain irradiation. Whole brain irradiation was found to be an effective means of palliating ovarian cancer metastatic to the brain, with symptomatic response achieved in 23 women, 16 of whom were palliated until death.

The role of selective irradiation in the management of recurrent or persistent ovarian cancer involving the vagina or rectum, after initial surgery or surgery with chemotherapy, was investigated by Firat and Erickson.¹⁶ Twenty eight women received selective irradiation and were evaluated for local control, survival and quality of life. Vaginal bleeding was controlled in all patients and a complete symptomatic response was achieved in 79% of symptomatic women. Vaginal bleeding or discharge can be palliated effectively in 71-90% of patients.¹⁷

Guideline - Radiation therapy for symptomatic relief and palliation	Level of Evidence	Refs
Symptomatic relief and palliation in women with metastatic or recurrent disease can be achieved with radiation therapy.	IV	15, 16, 17

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13. QUALITY OF LIFE AND PSYCHOSOCIAL ISSUES

BACKGROUND

Quality of life is a multi-dimensional construct that is generally accepted to include several important areas or domains of a person's life: physical functioning, psychological functioning, sexual functioning and spiritual and existential matters.^{1,2} There is support for the concept that cancer has a significant impact on all these major life domains.^{3,4} It has been suggested that using a brief, structured assessment of quality of life before a clinic appointment would be beneficial in identifying concerns in women with ovarian cancer.⁵

Key point:

- A brief structured assessment of quality of life before a clinical appointment may be beneficial in identifying concerns of a woman with ovarian cancer.

The diagnosis of ovarian cancer has a major impact on the quality of life of the woman, her family and friends. While there is evidence to support the use of psychosocial interventions to support the woman and to enhance her quality of life, the treatment team should not lose sight of the role played by the family and friends. Evidence from other cancers and chronic illnesses shows that family and friends can provide emotional and physical support and also provide an opportunity to discuss the disease and its impact.⁶⁻⁸

It is important for clinicians to be aware of the potential impact of the disease on women's quality of life and to have in place strategies for monitoring this, as there is evidence of the benefits of interventions. For example, a meta-analysis of 116 intervention studies showed that cancer patients receiving psycho-educational or psychosocial interventions had much lower rates of anxiety, depression, mood disturbances, nausea, vomiting and pain and, significantly greater knowledge about disease and treatment, than no intervention controls.⁹

Guideline - Psychosocial interventions	Level of Evidence	Refs
Psychosocial interventions can result in lower rates of anxiety and depression, reduced mood disturbances, nausea and vomiting and enhanced knowledge for cancer patients.	I	9

QUALITY OF LIFE ISSUES FOR WOMEN WITH OVARIAN CANCER

A Canadian study of older women's perspectives on living with ovarian cancer found that a significant difference was observed in quality of life before and after the diagnosis.¹⁰ Quality of life is likely to be significantly affected by both the symptoms of the disease and the side-effects of the chemotherapeutic agents used in treatment¹¹ with the severity of disease being cited as a crucial determinant of quality of life.¹²

The focus of management should be the minimisation of the physical and psychosocial impact of the cancer and its treatment, and promotion of optimal functioning. This is especially important in the case of metastatic disease. When ovarian cancer progresses, goals change from cure to prolongation of life, with the best possible quality of life for the patient.¹³

Key point:

- The focus of management should be minimisation of the physical and psychosocial impact of the cancer and its treatment.

Psychological interventions to provide support to ovarian cancer patients emotionally and to enhance their quality of life should be considered an important component of medical care. A multidisciplinary approach to cancer care that includes additional support, such as psychosocial counselling, could be beneficial.¹⁴ Interventions which have proven to be beneficial for other cancers include counselling,¹⁵ relaxation therapy,⁹ education programs¹⁶ and cognitive behavioural interventions.¹⁷ (See chapter 6 – *Multidisciplinary management of women with ovarian cancer*).

Support for women with ovarian cancer may also be found in groups such as peer support programs, telephone support programs and internet groups. (Refer to the *Clinical practice guidelines for the psychosocial care of adults with cancer*).¹⁸ The work of support groups in healthcare settings may be furthered by a multidisciplinary team approach, including psychiatry, social work, nursing and chaplaincy.¹⁹ In rural areas, the general practitioner can play a pivotal role in providing psychosocial support, as part of a multidisciplinary team.

Guideline - Psychosocial interventions that may be beneficial for women with ovarian cancer	Level of Evidence	Refs
Psychosocial interventions that can improve physical, functional and psychological adjustment and may be considered for women with ovarian cancer; include:		
• Counselling and relaxation therapy	I	9
• Education programs to improve pain control	II	16
• Cognitive behavioural interventions	III-2	17

SEXUAL ISSUES AND OVARIAN CANCER

Issues such as surgically-induced menopause, loss of child-bearing capacity, and the impact of a major life-threatening illness figure prominently in the psychological recuperation from ovarian cancer.²⁰ A survey of women with ovarian cancer, without evidence of active disease and not on treatment for at least 2 years, found that 57% reported that their sex lives had been negatively affected by cancer and its treatment. Women under 55 years of age reported a greater sense of loss about their sexual function and fertility.²¹ It is important to recognise that the impact on body image and sexual identity relates not just to the loss of body parts, but encompasses an altered sense of self as a social being.²²

Primary reanastomosis is always feasible following small bowel resection and is usually feasible following colonic resection. A stoma is a not uncommon issue for women with ovarian cancer. Evidence from colorectal cancer patients suggests that overall younger patients and women appear to experience higher levels of adjustment difficulties with a stoma.²³ It has been estimated that one-fifth of women whose sphincter function has been sacrificed suffer from dyspareunia.²³ For those patients who do not require a stoma but undergo ultra-low anastomosis, bowel and sexual function is also impaired.²⁴

A small, qualitative study in the United Kingdom²⁵ highlighted the need for healthcare professionals to be aware of concerns about sexual problems as they relate specifically to ovarian cancer. The recommendation from this study was that training be given to improve communication between women and their doctors in this area. A number of agencies provide communication skills training for doctors in Australia (*see Appendix 9*).

Key point:

- Doctors and other healthcare professionals should be aware of concerns about sexual issues as they relate specifically to ovarian cancer.

ANXIETY AND DEPRESSION

Data from a study of women with mainly advanced ovarian cancer suggest the need for an improved and more frequent assessment of ovarian cancer patients' psychological status, particularly as physical functioning declines, to improve early detection and referral for appropriate treatment.⁵ Impaired physical functioning was the most important predictor of heightened psychological distress, in an analysis involving medical/physical and socio-demographic predictors.⁵

Physiological stressors, such as surgically-induced menopause, steroid therapy and pain during active treatment, place women with ovarian cancer at high risk of depression and anxiety at this time.²⁶ It has been noted that clinically significant depression and anxiety may be more prevalent in patients with epithelial ovarian cancer than previously reported and that future studies of screening for and treating psychological distress are being designed to improve quality of life in these women.²⁷

A study of long term ovarian cancer survivors found that women continued to experience fear of follow-up diagnostic tests and fear of recurrence.²⁸ Another study reported that only one item, uncertainty about the future, negatively influenced quality of life.²⁹

A study of 60 women newly diagnosed with cervical, uterine and ovarian cancer found that the symptoms of depression experienced by women with ovarian cancer approached the level of acute symptoms typically reported by women entering outpatient psychiatric clinics.³⁰ Identification of those at risk of adverse psychosocial outcomes and its early detection and treatment is a crucial step in enhancing the quality of life of women with ovarian cancer.³¹

(Refer to 'Appropriate referral and specialised interventions for specific problems' –Table 5. Reproduced with permission, from the Clinical practice guidelines for the psychosocial care of adults with cancer).¹⁸

IMPACT ON THE FAMILY

Family members of newly diagnosed cancer patients report high levels of concern and psychological distress.³² Family studies where members have advanced cancer reveal that there may be significant anxiety, mood disturbance and poor mental health.³³ Psychiatric illness is reported in up to one-third of spouses and one-quarter of the offspring of men and women with advanced cancer.³¹ Although partners may feel highly anxious, only a small proportion actively seek out professional assistance.³⁴

Family reactions play a key role in the coping of women with cancer and promotion of more open communication and expression of feelings is generally helpful in adjustment.³¹

THE IMPACT ON HEALTH PROFESSIONALS

In dealing with oncology patients, many of whom have a poor prognosis, clinicians report experiencing frustration and a sense of professional failure.³⁵ Administering palliative or terminal care and a heavy work load have also been identified as contributing factors to professional 'burnout'.³⁵ Oncologists³⁵ and oncology nursing staff have reported high stress levels, with the levels being higher in those staff who are younger, who feel less supported in the ward,^{36,37} and more recent graduates.³⁸

Common sources of stress for clinicians are informing patients of the diagnosis of cancer³⁹ and providing emotional support for women and their families.⁴⁰ Decisions about complex and potentially toxic treatments⁴¹ and ethical and legal issues which arise in patient care add a further dimension of complexity to clinical work.

Clinical training often provides little preparation for the intensity of grief, anger, frustration and resentment displayed by patients and their families.⁴² Many clinicians may have unrealistic expectations about their role and how they cope. It has been found from areas such as Acquired Immune Deficiency Status (AIDS), that staff who have to

deal with the deaths of large numbers of patients faced an ‘accumulative loss’⁴³ and often feel immersed in suffering with little respite from the need to display warmth and empathy towards others.⁴⁴

It is also important for those working in oncology to be aware of and utilise the skills and expertise of members of multidisciplinary teams when dealing with complex clinical problems.⁴⁵ A study of breast cancer multidisciplinary teams in the United Kingdom found that teams with a number of leaders rather than just one, were most effective. The mental health of these team members was found to be significantly better than in other National Health Service (NHS) teams, those in previous studies of cancer clinicians and those in the general population.⁴⁶ One avenue for reduction of stress is enhancement of communication skills, as there is evidence that those who feel insufficiently trained in communication and management skills experience significantly higher levels of stress.⁴¹

Key point:

- Those who work in oncology should be aware of and utilise the skills and expertise of each member of a multidisciplinary team when dealing with complex clinical problems.

COMMUNICATION AND PROVISION OF INFORMATION

Women with cancer repeatedly report a desire to be well-informed.^{47,48} A Canadian study where 105 women from two university hospital oncology clinics were surveyed about their information needs, found that over 80% of these women wanted detailed information about ovarian cancer during the diagnosis, treatment and post-treatment stages of the disease and less than 1% wished for no explanation at any time point.⁴⁹ The top three categories concerning information were: the status and nature of the cancer, treatment concerns and self-care and empowerment issues.⁴⁹ (The authors noted that this sample consisted mainly of well-educated and urban women, but the issues of self care and empowerment should be considered for all women with ovarian cancer).

Effective communication involves more than the provision of information; it requires a process of individually-tailored explanation, problem-solving and acknowledgment of the woman’s feelings.

There are a number of communication skills that are relevant to any clinical situation and should be considered in any consultation with women with ovarian cancer. These are outlined below:

- Express empathy and listen effectively
- Avoid medical jargon and explain difficult terms
- Provide an interpreter if required
- Give clear specific information
- Actively encourage questions

- Actively check understanding
- Repeat important pieces of information
- Write down relevant information
- Tape the consultation as needed and if wanted
- Send a summary letter as follow up to both the woman and her treatment team

(Adapted from National Breast Cancer Centre's Psychosocial clinical practice guidelines: providing information, support and counselling for women with breast cancer.)⁵⁰

BREAKING THE NEWS ABOUT A DIAGNOSIS OF CANCER OR A RECURRENCE OF DISEASE

Breaking the news of a diagnosis or recurrence cancer can be difficult for both the woman and her doctor. For women with breast cancer it has been found that the way in which the news is given can affect the woman's understanding of the illness and impact on longer term psychological adjustment.⁵¹

Reaction to the diagnosis of a life-threatening illness has been accepted in the criteria for post traumatic stress disorder.⁵² Patients and families should be given time to assimilate information and the opportunity to ask questions and seek further information. One survey found that the diagnosis of persistent disease after conventional treatment for ovarian cancer proved more stressful for women than the diagnosis of the primary disease.⁵³ Some thought should be given as to how the news is provided, the setting and the woman's wishes in regard to support (see Cancer Council NSW booklet, *Breaking Bad News* 1997).⁵⁴

INVOLVEMENT IN DECISION MAKING

The National Health and Medical Research Council (NHMRC) notes that women with breast cancer are encouraged to make their own decisions about treatments or procedures and should be given adequate information on which to base those decisions.⁵⁵ Of women with ovarian cancer surveyed in two oncology clinics in Canada, the majority wanted to share cancer decision-making with their doctors - over 63% at diagnosis, 60% at treatment and 62% after treatment.⁴⁹

It is important to discuss with a woman the level at which she wants to be involved in decision-making. There may be some women who prefer to relinquish control over treatment decisions, particularly if faced with increasingly distressing and unfamiliar situations.⁵⁶ While some cancer patients with advanced disease and with a poorer health status were found to be least likely to seek involvement in their treatment decisions,⁵⁷ one study of women with ovarian cancer found that if the disease was perceived as very serious, or if metastases were present, women of all ages were much more likely ($p=0.001$) to prefer sharing decisions with their doctors, rather than autonomous or passive decision-making.⁴⁹

Key point:

- When ovarian cancer is perceived as being as very serious or when metastases occur, some women prefer to share decisions with doctors, rather than undertake autonomous or passive decision-making.

The following table is from the *Clinical practice guidelines for the psychosocial care of adults with cancer*.¹⁸

Table 5 Appropriate referral and specialised interventions for specific problems

Problem	Discipline to refer to	Specialised interventions with demonstrated effectiveness
Anxiety	Clinical psychologist/ Psychiatrist Social worker	Education; cognitive behavioural therapy including relaxation therapy or graded exposure; supportive psychotherapy (including existential therapy); crisis intervention; drug therapy; alone or in combination
Depression Suicidal ideation	Clinical psychologist/ Psychiatrist Social worker Psychiatrist	Education; cognitive behavioural therapy including problem-solving, and challenging negative cognitions; supportive psychotherapy (including existential therapy); often combined with antidepressant medication. In severe cases, ECT may be considered, or psycho-stimulants in those with advanced disease. Thorough assessment, identification and treatment of any specific stressors including pain, other physical symptoms, delirium. Treatment of identified depression, anxiety (see above)
Post Traumatic Stress Disorder (PTSD)	Clinical psychologist/ Psychiatrist	Cognitive behavioural therapy; supportive psychotherapy (including existential therapy), often in combination with antidepressants such as SSRIs
Body image concerns	Clinical psychologist/ Psychiatrist Social worker	Cognitive behavioural therapy; supportive psychotherapy; crisis interventions; complementary therapies, eg Exercise. Treatment of depression or anxiety which can compound the body image disturbance

Table 5 (contd)

Problem	Discipline to refer to	Specialised interventions with demonstrated effectiveness.
Sexuality concerns	Clinical psychologist/ Psychiatrist Social worker Endocrinologist	Personal and or couples counselling Endocrine assessment and or therapy if hormonal basis for the problem appears likely
Inter-personal problems	Clinical psychologist/ Psychiatrist/ Social Worker	Couples counselling; family counselling
Severe emotional problems	Clinical psychologist/ Psychiatrist	Cognitive behavioural therapy; supportive psychotherapy
Physical symptoms	Clinical psychologist/ Psychiatrist Other specialists	Education; cognitive behavioural therapy including relaxation therapy, guided imagery; supportive psychotherapy; speech therapy, physiotherapy, occupational therapy, nutritional services, dentistry, endocrinology, reconstructive surgery, specialist pain services, odour management
Fertility concerns	Clinical psychologist/ Psychiatrist Endocrinologist Fertility clinic/ Women's Health Nurse/Family Planning	Personal and or couples counselling Hormone assessment and or therapy Fertility counselling, storage of ovarian tissue/ oocytes/embryos and sperm, in vitro fertilisation

Notes:

In addition to the specialities listed above, there may be other local practitioners trained in the interventions listed eg. occupational therapists, specialist nurses. Many general practitioners will also have training in the above interventions.

For women experiencing sexual concerns referral to a gynaecologist/urologist is also recommended because of all the practical issues involved.

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14. ALTERNATIVE AND COMPLEMENTARY THERAPIES

The term ‘alternative therapies’ is used loosely to describe ‘anything outside the orthodox circle of surgery, radiation and chemotherapy’.¹ It can be used to cover a number of different approaches such as diet therapy, vitamins, herbs, relaxation, meditation and acupuncture (*see chapter 16 – Palliative Care*). However, an approach such as relaxation or meditation, which can work alongside conventional therapies, is usually known as a complementary therapy. The effect of many alternative therapies is unknown, and some may in fact cause harm. Most have not been examined rigorously, and some of those that have been examined have not been found effective.^{2,3,4}

Key point:

- There is little evidence that alternative therapies are effective in treating cancer.

Some complementary therapies, such as relaxation and meditation, have been shown to be effective, or at least not harmful, by conventional medical standards.⁵ Both relaxation and meditation are frequently and effectively used by general practitioners and palliative care teams. Complementary therapies, which concentrate on the mind-body relationships, such as prayer, laughter, relaxation and meditation, have been tested in the USA, through the National Institutes of Health, Office of Alternative Medicine and have been shown to be effective or valuable.^{6,7,8} There is evidence from randomised trials to support the value of hypnosis for cancer pain and nausea; relaxation therapy, music therapy, and massage for anxiety; and acupuncture for nausea.⁹

Guideline - Relaxation therapy	Level of Evidence	Refs
Relaxation therapy has been shown to be effective and non-harmful in managing patients with cancer pain.	I	5

Both alternative and complementary therapies are used by many Australians. Women are significantly more likely to use alternative products than men, especially vitamin and mineral supplements, evening primrose oil, aroma therapy oils and homeopathic medicines.¹⁰ Both in Australia and overseas, studies have demonstrated that up to 54% of adults with cancer use alternative therapies.^{11,12,13,14,15}

Amongst the users of alternative therapies in the study by Begbie *et al.*¹¹ the main reasons for using alternative therapies were:

- a new source of hope (49%);
- a preference for natural therapy (40%);
- the impression that it is a non toxic therapy (37%);
- a supportive alternative practitioner (29%);
- to try something different (23%); and
- a sense of greater personal involvement (14%)

The therapies often used by those using alternative therapies ¹¹ were:

- relaxation / meditation (59%);
- diet therapy (57%);
- megavitamins (43%);
- positive imagery (44%);
- aith/spiritual healing (30%);
- naturopathy (27%);
- immune therapy (17%);
- homeopathy (16%); and
- acupuncture (11%)

Seventy-five percent of people using alternative therapies used more than one (median 3, range 1-8).¹¹

USE OF ALTERNATIVE AND COMPLEMENTARY MEDICINE BY WOMEN WITH GYNAECOLOGIC CANCERS

A small American study (based on telephone interviews of women identified from a gynaecologic clinic) found that 51% of women had taken herbs sometime since they were diagnosed with ovarian cancer. Most herb use occurred concurrently with chemotherapy. Only 12% of women used a herbalist or other health practitioner for guidance in the use of the herbs.¹⁶

An outpatient study in a Midwestern university looked at use of complementary and alternative therapies (CAT) by patients with gynaecologic cancers over a 3 month period, using an anonymous questionnaire. There were 113 respondents. Of these 60% were being treated with chemotherapy with or without radiation therapy. Fifty-six (49.6%) had used CAT since their diagnosis. As expected, many women used multiple types of CAT, with 46% ingesting some kind of CAT. Products ingested included herbal therapies and plant extracts, high-dose vitamins and/or minerals, medicinal teas and shark cartilage.

Forty-four women (79% of users) used a psychological or spiritual therapy. The most common answer written in on the questionnaire was prayer. The majority of users hoped to achieve some benefit from CAT as an alternative therapy to directly fight the cancer (36%) or to increase the body's ability to fight the cancer (64%).¹⁷

COMMUNICATION ISSUES

Many cancer patients using alternative therapies do not discuss it with their doctor.¹¹ Presumably these patients are not asked or choose not to tell their doctors. It can be assumed that a negative attitude from health care providers about alternative therapies will inhibit frank discussion. Such inhibition means that women will not learn of support of, or concerns for, the way in which the alternative or complementary therapies may affect the conventional treatment patterns.

It has been suggested that doctors of women with gynaecologic cancer should ask these women early about CAT usage, during the initiation of cancer care.¹⁷ This could increase awareness of the potential for herb-drug interactions, such as the effect on chemotherapy and clarify the reasons why patients are using CAT. It may be able to shed light on issues not being addressed to the patient's satisfaction. 'An oncologist is likely to increase personal rapport and encourage patient trust by discussing this common practice'.¹⁷

Key point:

- **It is important for the clinician to be aware of all medication the patient is taking, to avoid adverse interactions with drugs.**

For many women, feeling that they can assume some control of the treatment of their disease is psychologically empowering. The physical problems that may arise from interference with conventional therapies may be attenuated by the strong psychological value of the alternative therapy. If conventional therapy holds little hope of cure for women, it is understandable that they seek other solutions. Clinicians should also be aware that the decision to use alternative therapies may not be based on the same philosophical approach as that used by their health care providers.

It is to everyone's advantage if women are able to discuss alternative therapies openly, knowing that they will continue to receive support and understanding from their health care providers, whether or not they agree with the therapy being used.

Key point:

- It is advantageous for a woman with ovarian cancer to be asked about her use of alternative and complementary treatments. This is even more important for women advanced and recurrent disease, as they may turn to these treatments when other conventional treatments fail to cure the disease.
- It is important for the clinician to be supportive of women taking alternative therapies, within the context of cost and safety issues.

SAFETY ISSUES

There are safety issues to be considered in the use of therapies that alter diet or introduce supplements into the diet. While the content of some substances is uncontrolled and has not been tested for safety, some may be intrinsically toxic. The safety of megavitamins, particularly those that are the fat-soluble has been questioned and there is the potential for high doses of vitamin A to cause headaches due to raised intracranial pressure.¹⁸

COST

The cost of alternative therapies needs to be explored with the woman. In a study in South Australia,¹ mean monthly expenditure on alternative therapies was \$10, with a range of \$1-\$500. However, some therapies are very expensive and the patient may be required to pay the full cost with no government subsidy/health fund rebate (*see chapter 18 – Economic implications for guideline implementation*).

(Adapted with permission from the National Breast Cancer Centre. Clinical practice guidelines for the management of advanced breast cancer.)¹⁹

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15. FOLLOW UP

FOLLOW UP POST-TREATMENT IN WOMEN WITH EPITHELIAL OVARIAN CANCER

Follow up is designed to provide appropriate medical review to support the physical and emotional needs of women following treatment. It can also establish a conduit through which a woman can communicate with an expert about her current health status, psychological issues, and the experience of the cancer journey. A definitive program is useful in providing this level of support. Women with ovarian cancer expect such a program, to offer continuity and support, regardless that the disease stage at diagnosis is predominantly advanced, and that the ultimate prognosis is usually poor.

The options for follow up, and the implications and possible consequences of these options should be discussed with the woman at the completion of the primary treatment. This discussion should include the option of no follow up. Some women will decide that the psychological trauma of follow up is too unsettling and opt to come only if they have symptoms. Others will be keen for surveillance – even though they may experience great anxiety prior to the follow-up visits.

There should also be time provided for personal discussion with the clinician about the implications of monitoring progress using CA125. The implications of stable, fluctuating and rising levels of CA125 should be discussed.

SURVIVORSHIP ISSUES

Some women who survive ovarian cancer, or who are living with ovarian cancer, have reported positive changes such as a new appreciation of life, a strengthening of relationships or family ties or a more “live for the moment” philosophy.¹ However, many women report issues related to survival. A small study of 18 Canadian women living with ovarian cancer, found that the most significant challenges faced by women with ovarian cancer could be grouped into three main themes: living with uncertainty, the stigma of cancer and facing death.²

The members of the treatment team should be aware that follow up visits may be a source of anxiety for women, with concerns about the testing involved and the possibility of a recurrence being diagnosed. Women surveyed about their experiences of recurrent disease have described the experience of waiting for a recurrence as frightening and the follow up appointments were anticipated with fear that their ovarian cancer had recurred. Tumour markers such as CA125 were a signal that their cancer was recurring and they found the periods of waiting difficult. A rising CA125 had significant meaning, and triggered panic, profound fear and devastation knowing it meant a recurrence of the cancer.³

In a study of women with stage I and II ovarian cancer, who had survived 5 years or more after completion of treatment, survivors reported significant amounts of distress related to fear of a second cancer, recurrence of the cancer, and future diagnostic tests. In relation to specific survivorship stressors, 18% reported continuing distress since the completion of treatment, and distress related to changes in their appearance as a result of the cancer and/or treatment.⁴ The diagnosis of persistent disease after treatment has been found to be more stressful for women than the initial diagnosis.⁵

TIMING OF FOLLOW UP CONSULTATIONS

COMMON PROGRAM

A woman may be reviewed by either a gynaecological oncologist or medical oncologist. If it is convenient for the woman, she may see her gynaecological oncologist and medical oncologist at alternate visits. The important factor is that follow up be offered regularly. There is no recommended frequency of follow up consultations, but a clear and mutually agreed arrangement, which acknowledges the benefits of an ongoing relationship and the opportunity to deal with issues as they arise, should be negotiated with the woman.

A common follow up program is:

- Review every 2-3 months for 2 years then;
- Review every four months for the next 2 years; and
- Review 6 monthly for a year before moving to annual review.^{6,7}

Key point:

- It is important that a clear and mutually agreed follow up routine be provided at appropriate intervals to all women who have been treated for epithelial ovarian cancer.

FORMAT FOR FOLLOW UP CONSULTATIONS

The basic format of consultation is to have the history updated, physical examination including pelvic examination undertaken and blood taken for CA125 cancer marker. In those women who initially had an elevated CA125, relapse of tumour can be accurately identified by the measurement of CA125 and this may be done at each visit.^{6,7,8} It should be noted that the woman's report to the clinician about how she feels will often contain the best index of recurrence for the clinician.

Radiological imaging should not be done routinely, but should be performed if there is clinical or CA125 evidence of recurrence. The rationale for not undertaking imaging should be discussed with the woman.

Key point:

- The CA125 level is an accurate predictor of relapse of epithelial ovarian cancer in those women who initially had a significantly raised CA125.

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16. PALLIATIVE CARE

PALLIATIVE CARE

Hospice and palliative care has been defined as a concept of care which provides coordinated medical, nursing and allied services for people who have a terminal illness, delivered where possible in the environment of the person's choice, and which provides physical, psychological, emotional and spiritual support for patients and for patients' families and friends. The provision of hospice and palliative care services includes grief and bereavement support for the family and other carers during the life of the patient, and continuing after death,¹ where appropriate.

Palliative care:

- stresses advanced planning rather than crisis intervention;
- offers a multidisciplinary model of care which is focussed on the whole person within their social and emotional context, rather than just the one disease; and
- requires a good knowledge of the natural history of the disease and relevant oncological practice.²

Ovarian cancer may affect women of all ages; including some women as young as in their 30s and 40s, creating additional distress in all areas. It is therefore desirable that there is an opportunity for early referral for psychological, emotional and social support for all women. Early attention to symptom control may alleviate many other problems which can cause distress.

The natural history of ovarian cancer, especially for women with stage III, stage IV and recurrent disease, is that there will be one or several remissions with therapy, before the final failure of treatment. Ovarian cancer frequently behaves as a chronic disease, with periods of disability and improvement, and a later final period of severely diminished personal function, prior to death. Thus, although cure may not be a realistic aim, significant long-term remissions mean that treatment should be recommended.

Key points:

- The history of advanced ovarian cancer is usually of one or several remissions to therapy before finally failure of treatment.
- Early attention to psychosocial support is important.

ORGANISATION OF PALLIATIVE CARE

Palliative care services have evolved in variety of ways, but in metropolitan areas specialist consultant palliative care services are generally available to give advice on symptom control and other problems, both in hospital and in the community. Access to hospice or specialist palliative care beds is also generally available.

In rural and remote areas access to specialist palliative care is limited. General practitioners will be able to supply significant support, further consultations may be by telephone or video conferencing and access to specialist inpatient care may be limited by distance.

Most palliative care will be provided by the existing network of carers, co-ordinated by either the general practitioner and/or treating gynaecology oncologist, who will draw on other health professionals as particular expertise is required. The National Strategy for Palliative Care encourages the use of existing networks and community services, working with palliative care specialists, to deliver palliative care.³

As the availability of specialist palliative care increases, and particularly with complex or difficult to resolve issues, specialist palliative care teams should be utilised to achieve optimum outcomes for the woman with ovarian cancer. Good communication at all times between all members of the treating team is essential.

The involvement of a specialist palliative care team in the care of patients with cancer in general increases patient and carer satisfaction, increases the amount of time spent at home by patients, reduces the time spent in hospital, reduces the overall cost of care and increases the likelihood of the patient dying where they wished to be.⁴

Guideline - Specialist palliative care services	Level of Evidence	Refs
Specialist palliative care services can improve outcomes in relation to patient satisfaction, patients being cared for in their place of choice, family satisfaction and control of pain, symptoms and family anxiety.	I	4

TIMING OF REFERRAL

Early referral will often be helpful. The precise timing at which the services of a palliative care specialist are introduced will depend predominantly on the patient's wishes, the individual illness, its varied symptom complexes; and psychosocial factors. Referral is facilitated if the palliative care professionals are already an integral part of the multidisciplinary treatment team.

Benefits from early referral include allowing the establishment of personal contact and exploration of options for future care, without any imperative for immediate decisions. This stresses active advanced planning, rather than crisis intervention.

The involvement of palliative care services does not preclude, and will frequently support, the continuation or commencement of active treatment programs.

Symptom relief, personal and family support and death preparation are a part of the care plan from the time of diagnosis, not merely introduced when active therapy options are not working.

SYMPTOM RELIEF

The principles of symptom control include:

- assessment of the symptom, including understanding the meaning ascribed by the patient. (This requires active listening on the part of the clinician, with allowance made for cultural factors);
- explanation of the likely cause;
- investigations (should be reserved for situations where a decision is required about continuing the same treatment plan or making a change);
- institution of treatment based on the known or likely causes of the symptoms, available options for treatment, and the wishes of the patient; and
- monitoring of the response to treatment and modification as necessary.

There is no set model of symptoms and progression of disease. In some cases, functional disturbance may precede structural change, as proven by clinical signs or radiological evidence of disease progression, but equally the reverse may apply, where an elevated tumour marker may precede by several months any objective evidence of recurrent or progressive disease.

Physical symptoms that are commonly reported in ovarian cancer are:

- Pain
- Fatigue
- Degrees of nausea and vomiting and constipation, culminating in malignant bowel obstruction
- Abdominal distension (from tumour, ascites or distended bowel)
- Dyspnoea (from pleural effusion or splinting of the diaphragm)

For guidelines on the management of symptoms not specifically addressed here, refer to *Therapeutic Guidelines: Palliative Care* (1st edition, Sept, 2001).⁵

PAIN

Over 70% of people with terminal cancer experience pain. Except in rare cases, cancer pain should be treatable.⁶ The pain management plan should aim to achieve pain relief both night and by day, at both rest and on movement.

Key point:

The pain management plan should aim to achieve pain relief both night and by day, at both rest and on movement.

It may include pharmacological and non-pharmacological methods. Some patients will benefit from non-pharmacological methods of pain relief such as relaxation⁷ or acupuncture.

Best care is provided when the woman and her family are offered as much information as possible about the cause of any pain experienced, and all help should be given to ensure that they understand and accept the recommended management plan. The management plan will need to include instructions for dealing with breakthrough or exceptional pain. All members of the treatment team should be aware of the management plan, to ensure a consistency of approach. As part of the plan, the woman and her supporters will need to be made aware of the mechanism for continued assessment and the follow up that is available. The details can be written down, if necessary.

RELIEF OF PAIN

If oral medications for pain have been in use, the route should be changed to a parenteral one. The subcutaneous route is frequently used for morphine, fentanyl or hydromorphone. Transdermal fentanyl¹ could be considered once stable pain control has been achieved and if the dose range is suitable.

RELIEF OF COLIC

Colicky pain may be a feature. Hyoscine butylbromide can be used subcutaneously. Its anti-cholinergic action may be helpful in reducing secretions and therefore reducing vomiting.

PAIN NOT CONTROLLED BY CONVENTIONAL ANALGESIA

The use of co-analgesics, nerve blocks or epidural delivery of analgesics, managed by a specialist in palliative care or pain management should be considered for women with uncontrolled pain.⁸

(For further information on the management of acute and severe pain in patients with cancer, see: *Acute pain management: scientific evidence.NHMRC.1998*⁹ and *Management of severe pain*. NHMRC. AGPS. 1998).¹⁰

BOWEL OBSTRUCTION

Bowel obstruction is a frequent complication of ovarian cancer, occurring in 15% -25% of patients overall, and in 45% of patients with advanced ovarian cancer. In localised disease, surgery may be considered, but the usual pattern of widespread peritoneal and omental disease leading to multiple sites of obstruction usually precludes this approach.

Medical management of bowel obstruction may include:

- **Relief of nausea and vomiting**

If obstruction is incomplete, use of a prokinetic anti-emetic such as metoclopramide can be considered as well as manoeuvres to clear the lower bowel of faecal material. If obstruction is complete, a centrally acting anti-emetic is recommended such as haloperidol (S/C) or prochlorperazine (PR).

- **Rehydration**

If the volume of loss can be reduced, reasonable levels of hydration for comfort can be maintained with S/C normal saline, 1 litre/24 hours, which can still allow care at home.¹¹

High dose steroids (S/C dexamethasone for 3-5 days) have been tried but there are no conclusive studies of efficacy.¹²

Octreotide has been used to reduce secretions and therefore reduce vomiting (or allow removal of nasogastric tube if one has been inserted).¹¹

- **Venting Gastrostomy**

In patients where vomiting is the major symptom, there may be a role for venting-gastrostomy. This can offer the patient a good quality of life, without vomiting or a nasogastric tube, as well as the possibility of eating and drinking for enjoyment, but not nutrition.¹³

ASCITES

Ascites continues to be an unsolved problem. Mechanical relief is often unavoidable, but is time limited, not least because of loss of protein.

Anecdotal mention of spironolactone, with or without steroids, may slow the rate of accumulation of ascites.

Evidence for shunting procedures is sparse, and experience is varied. The Le Vein shunt has been used in a series in Adelaide. The criteria for use have included:

- high production rate - at least one litre weekly;
- no particulate matter (i.e. bloody or chylous ascites);
- life expectancy of at least 2 months.

(For further information also see *Appendix 5*).

PERSONAL AND FAMILY SUPPORT

Both the woman and her family will need physical, emotional and psychosocial support during the course of her illness, but the extent or nature of that support will vary for a number of reasons, including the impact of the disease on functioning, psychological adjustment, individual differences in coping and the strategies used. Support may be provided by other members of the family, friends, members of the treatment team, peer group programs or through access to telephone or Internet programs.

(For further information about support services see *Appendix 9* and the *Clinical practice guidelines for the psychosocial support of adults with cancer*).¹⁴

DEATH PREPARATION

Death preparation involves initial recognition of imminent death (by patient, family, doctor) as a possible or likely outcome, which gives a perspective on:

- the value of time;
- priorities for action; and
- balancing losses and gains.

If the disease is clearly progressing, despite the best therapeutic efforts, the focus should change to death preparation, with strong emphasis on achievement of goals and ambitions and planning for later critical events, during a time when the patient's perspective is clear and well understood.

Prolongation of life strategies needs to be tempered by measures to maintain and improve quality of life by controlling functional disturbances caused by the cancer and by good symptom control. In some cases, when the disease has progressed faster than expected, the woman and her family may have some issues not completely resolved, such as regret about the late diagnosis.

On the death of the woman, a formal letter of condolence from the treating clinician is important in facilitating active bereavement.

Key points:

- Prolongation of life strategies needs to be tempered by measures to maintain and improve quality of life by controlling functional disturbances caused by the cancer and by good symptom control.
- On the death of the women, a formal letter of condolence from the treating clinician is important in facilitating active bereavement.

(For further information about end-of-life issues see the *Clinical practice guidelines for the psychosocial care of adults with cancer*).¹⁴

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17. CLINICAL TRIALS

The treatment of ovarian cancer is an evolving area and important clinical questions remain unanswered in the areas of surgery, chemotherapy and radiation therapy, at all stages from early disease to relapse. The gold standard test for new treatments must remain the randomised controlled trial. Clinical trials help to define new standards of care and are critical to improving standard therapy. The introduction of novel, target directed anticancer therapies requires new study designs as the phase I/II/III paradigm may not be relevant. Relapsed disease is seen as an important area for randomised controlled trials.¹

It has been noted that quality of life is an important end point,¹ although it is cautioned that quality of life measure in clinical trials should be interpreted carefully. All new clinical trials will include quality of life measures.

CLINICAL TRIALS

Clinical trials usually involve the testing of new treatments, or of new indications for treatments established for other indications. The development of a new treatment involves progression through three phases of clinical trials:

- Phase I trials are designed to evaluate the relationship between dose and toxicity, and aim to establish a tolerable schedule of administration. They usually include only small numbers of patients who have already received the standard treatments for their condition.
- Phase II trials are designed to screen new treatments for their anti-tumour effects, in order to identify those worthy of further evaluation. In phase II trials, a series of patients with a particular type of cancer receive the new treatment to determine the proportion in whom the tumours will shrink. If this proportion of patients responding compares favourably with other available treatments, then the usefulness of the treatment in patient management is assessed in a phase III trial.
- In phase III trials, patients are randomly allocated to receive either the new treatment or the best available standard treatment. Ideally the two arms of the treatment should be indistinguishable, so if possible an inactive placebo is used to mask the standard treatment arm. This is rarely possible in trials of chemotherapy drugs due to their side effects.

In Australia clinical trials must be approved by an Institutional Ethics Committee. Women must be provided with relevant information and complete information about the trial protocol and provide their written consent before they take part. Entry into a trial must be voluntary and refusal to enter a trial or a decision to withdraw later without giving a reason must not affect the woman's relationship with her treating practitioner.

(Acknowledgement: Clinical practice guidelines for the management of advanced breast cancer. National Breast Cancer Centre. 2001).²

PARTICIPATION IN CLINICAL TRIALS

Currently, only a few of all the patients suffering from any cancer participate in clinical trials. This may be a reflection of a lack of awareness by both clinicians and patients, although not all patients offered participation in a trial take part, commonly citing that they fear being used as a 'guinea pig'.

A participant survey conducted by the Coalition of National Cancer Cooperative Groups Survey in the USA (1998) showed that 85% of patients were not aware of the existence of clinical trials and that participation was an option.

The doctor most frequently does not offer the opportunity of participation. This may be because of a lack of awareness of the existence of the trial, or some clinicians fear that trial participation denies them individual clinical autonomy.

While the possibility of selection bias should be noted³, there is some indirect evidence to suggest that participation in clinical trials results in better outcomes when compared to patients given a similar treatment outside a clinical trial setting.^{4,5,6} This advantage is independent of stage. Treatment adherence may be sub-optimal outside the quality assurance framework of a clinical trial.

Guideline - Clinical trial participation	Level of Evidence	Refs
Cancer patients who participate in clinical trials may have better outcomes than those given the same treatment outside a clinical trial setting. It is appropriate for clinicians to discuss participation in clinical trials with women who have ovarian cancer.	III-I	4

Better outcomes may be due to:

- increased quality control mechanisms within the framework of controlled trials;
- standardised procedures;
- independent data review; and
- early relapse detection and treatment.

Patients who were surveyed by the Coalition of National Cancer Cooperative Groups and were treated as part of a trial reported this as a positive experience, and that the role of the doctor was pivotal to recruitment.

- 98% reported that they had received excellent care and were treated with dignity and respect, and that they viewed trial participation as a positive experience;
- 82% were happy that they did not perceive that they were treated as guinea pigs, nor were there unnecessary tests; and
- 78% would recommend trial participation to others.

When asked about their reasons for participating in a trial:

- 75% felt they were accessing best quality care;
- 62% cited that they were gaining access to newer or better treatment;
- 70% were happy to benefit others; and
- 40% felt that they got more care and attention.

The major focus of both the medical and consumer groups is to examine the overall value to the individual patients of participation in a clinical trial and comparing their survival rates with those patients treated outside trials with currently recognised standard therapy.

SOURCES OF INFORMATION ABOUT CLINICAL TRIALS

Information about clinical trials is available to patients and clinicians through a number of sources. The information provided covers aspects such as an explanation of clinical trials and issues of consent, as well as providing details of specific clinical trials being conducted.

Information may be obtained from:

- Australian and New Zealand Gynaecological Oncology Group (ANZGOG)
- National Health & Medical Research Council (NHMRC) Clinical Trials Centre
- Database of Cancer Research in Australia (CARA)
- The Cancer Council Australia
- State and Territory Cancer Councils
- Peter MacCallum Cancer Institute

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18. ECONOMIC IMPLICATIONS FOR GUIDELINE IMPLEMENTATION

While little formal research has been undertaken in relation to the costs of epithelial ovarian cancer, its economic impact would appear to be significant, particularly as so many cases are diagnosed too late for cure to be achieved. Economic factors can be identified in relation to direct and indirect costs, and to loss of quality of life and of loss of life itself. Due to the lack of economic data at this time, it may be useful to consider the economic impact of ovarian cancer in terms of present costs and then of future costs and benefits.

The first consideration of present costs relates to lives lost and to life years lost. Whatever measure is used, the costs of lost productivity include estimates of the value of paid work and the value of unpaid work, such as work in the household and voluntary work. These costs relating to women with ovarian cancer are borne by society.

An important component of present costs are treatment costs, which include medical and hospital services, drugs eg chemotherapy recommendations and tests, for example, those relating to surgical staging. These costs are primarily borne within the health care system, although co-payments and indirect costs such as time for treatment are borne by the patients themselves. The direct health care costs of malignant ovarian cancer were AU\$13.5 million in the 1993/94 financial year. Hospital costs were by far the greatest proportion (87%) of the direct costs of ovarian cancer in 1993/1994. This figure also includes medical services, pharmaceuticals, and allied health services. If all ovarian cancers are included (malignant, benign, in situ and uncertain) the cost was AU\$31.3 million. Ovarian cancer is estimated to be the fourteenth most costly cancer to treat with an estimated lifetime cost of nearly AU\$13,000 per new case.¹

Another component of present costs is that related to alternative and complementary therapies. While alternative and complementary therapies are widely used by people with cancer, there is very little information available on expenditure on alternative and complementary products and services. These costs are almost all out-of-pocket and borne by patients. In 1993 Australians spent an estimated AU\$309 million per year on alternative therapists and AU\$621 million per year on alternative therapies, which exceeds the patient contribution of AU\$360 million to standard pharmaceuticals in 1992/1993.² (*See chapter 14 – Alternative and complementary therapies*)

Current costs which have not been sufficiently documented include costs of home care provided by health professionals and informal care provided by family and friends,³ including time lost from employment when accompanying the woman with ovarian cancer to medical appointments.

FUTURE COSTS AND BENEFITS

When effective screening tests become available, economic evaluation will be required, including identification of the most appropriate target population, to ensure optimal use of resources. From an economic perspective, no implementable prevention strategies have yet been identified, so no prevention cost estimates are yet possible. Future

costs for best practice will include support for clinical trials, for example relating to radiation therapy. The development of national databases to provide comprehensive and consistent data should be accompanied by cost/benefit analysis.

IMPLICATIONS FOR IMPLEMENTATION

The implementation of the *Clinical practice guidelines for the management of women with epithelial ovarian cancer* may impact on future health care costs in a number of areas:

- the training of gynaecological oncologists (*see chapter 6 – Multidisciplinary management of women with ovarian cancer and Appendix 4, Gynaecological oncology training requirements*);
- the provision of nurses with appropriate skills in the area of gynaecological cancer (*see chapter 6 – Multidisciplinary management of women with ovarian cancer*);
- the establishment of multidisciplinary care centres or the development of facilities to support access to the expertise of multidisciplinary care teams through methods such as video conferencing (*see chapter 6 – Multidisciplinary management of women with ovarian cancer*);
- the training of specialist gynaecological pathologists (*see chapter 5 – The biology and pathology of ovarian tumours*);
- the cost of establishing centres for education and research in the histopathology of rare and variant ovarian tumours (*see chapter 5 – The biology and pathology of ovarian tumours*);
- the cost of tests to confirm diagnosis of rare and variant ovarian tumours (*see chapter 5 – The biology and pathology of ovarian tumours*);
- the conduct of clinical trials of different treatment modalities such as chemotherapy and radiotherapy (*see chapter 17 – Clinical trials*);
- the provision of home support where a woman with ovarian cancer has a young family and;
- the provision of financial support when a woman with ovarian cancer is no longer able to work (*see chapter 13 – Quality of life and psychosocial issues*).

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