RESEARCH

Ovarian cancer: patterns of care in Victoria during 1993–1995

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ABSTRACT

Objective: To describe the management of and outcomes in patients with newly diagnosed ovarian cancer during 1993, 1994 and 1995 in Victoria.

Design and setting: Retrospective cohort study conducted by surveying doctors involved in managing incident ovarian cancer cases identified from the population-based Victorian Cancer Registry. The survey was conducted in 1997 and the cohort was followed up until the end of 1999 to obtain at least four years of follow-up data on all patients.

Patients: All women with invasive epithelial ovarian cancer diagnosed during 1993, 1994 and 1995.

Main outcome measures: Reported management in terms of staging, treatment and survival.

Results: Management details were obtained for 84.5% (562/665) of eligible patients. Median age at diagnosis was 66 years (range, 22–98 years). Surgery was the primary therapy in 77.2% of women (434/562). Only one in three women had adequate surgery, which was less likely to be performed by general gynaecologists and general surgeons than gynaecological oncologists (21.3% [35/164] v 13.3% [8/60] v 52% [105/202]). After surgery 78.6% of women (341/434) received chemotherapy, usually with platinum-based regimens. The overall five-year relative survival was 46% for women treated surgically; poor survival was related to increasing age, later tumour stage, presence of ascites, residual disease >2 cm and poorer histological differentiation of the tumour.

Conclusions: For optimal care a preoperative carcinoma antigen (CA)-125 assay, chest x-ray and pelvic ultrasound should be performed, and early referral to a multidisciplinary unit for definitive surgery is advised. Every effort should be made to adequately stage or debulk the tumour. Women with high-risk early-stage and advanced disease should be considered for platinum-based chemotherapy.

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In Victoria, ovarian cancer is the sixth most common cancer in women, with an age-standardised incidence and mortality of 11.8 and 5.4 cases per 100 000 women, respectively.[1] The reported five-year survival for early-stage disease ranges from 50%–90%, and for late-stage disease from 55%–20%.[2,3] The prognosis is worse in older women, those with advanced stage, ascites and poorly differentiated tumours or clear-cell adenocarcinoma. Poor prognoses are also associated with preoperative tumour rupture and dense adherence in early-stage disease, and with bulky residual tumour after surgery in advanced disease.[4]

The Victorian Cancer Registry (VCR), in collaboration with the Victorian Cooperative Oncology Group, has been used as a sampling frame for conducting population-based surveys of cancer management. The concern that patients with ovarian cancer may not undergo adequate surgical staging and multidisciplinary management prompted our survey to determine how women were managed with respect to preoperative investigations and adequacy of staging and treatment, in addition to all-cause and relative survival at five years from diagnosis.

METHODS

A population-based sample of all women with ovarian cancer diagnosed during the years 1993 to 1995 was identified from the VCR. Treating doctors were sent a questionnaire relating to the management of each patient. The survey was sent in June 1997 and the sample followed until December 1999 to obtain outcome details for a minimum of four years of follow-up.

Non-epithelial and borderline (low malignant potential or proliferating) epithelial ovarian tumours were excluded from analysis. One author (M A Q) reviewed individual pathology reports to clarify inconsistencies in cancer stage, but independent histological review was not performed.

Women with early-stage disease were considered to have had adequate staging surgery if total abdominal hysterectomy and unilateral or bilateral salpingo-oophorectomy, multiple peritoneal biopsies, peritoneal washings, infracolic omentectomy, and pelvic and para-aortic lymph node sampling were completed.[5] Women with late-stage disease were considered to have had adequate surgery if they had undergone optimal debulking or cytoreduc-

For editorial comment, see page 4.

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1: Stage definition and recommended management

FIGO* stage	Definition	Adequate surgery	Chemotherapy
Early-stage disease			
Ia	Tumour limited to one ovary	Total abdominal hysterectomy, omentectomy, multiple peritoneal biopsies, peritoneal washings, and pelvic and para-aortic lymph node sampling	Platinum and taxane combination in selected patients (ie, histology poorly differentiated/clear cell morphology or densely adherent)
Ib	Tumour limited to both ovaries		
Ic	Tumour limited to one or both ovaries with any of the following: capsule ruptured, tumour on ovarian surface, malignant cells in ascites or peritoneal washings	As above	Yes — platinum and taxane combination
II	Tumour involves one or both ovaries with pelvic extension (direct extension or implants to uterus, other pelvic tissues)		
Late-stage disease			
III	Tumour involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph node metastasis	Optimal tumour debulking to <2 cm residual disease	Yes — platinum and taxane combination
IV	Distant metastasis		

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tion of the tumour to residual disease <2 cm.

Statistical analysis

Descriptive statistics were analysed with the SPSS statistical package.[6] All cases were followed up through the VCR and death tapes from the Registrar of Births, Deaths and Marriages and the National Death Index for a minimum of four years. Relative survival proportions were derived by the actuarial method to calculate expected survival and proportional hazards regression to model the relative survival.[7] The initial and terminal events from which survival was calculated were diagnosis date and date of death from any cause. No cases were censored; it was assumed that women not known to have died in Australia were still alive. Relative survival proportions were computed separately for each prognostic indicator. This method adjusts the survival proportions for the other causes of mortality associated with age using Victorian life-tables. A multivariate analysis was then performed. Specific relative risks (RR) with 95% confidence intervals were calculated from the regression coefficients of the proportional hazards model for subgroups of women in the study by prognostic factors (eg, stage, age group, tumour grade) and treatment-related factors (eg, chemotherapy, treating specialist, adequate surgery).

Ethical approval

The Anti-Cancer Council of Victoria Institutional Ethics Committee approved the survey proposal.

RESULTS

After excluding 225 women (whose histology results indicated borderline or non-epithelial tumours), completed questionnaires were received for 562 of 665 patients (84.5%) with invasive ovarian carcinoma.

Median age at diagnosis was 66 years (range, 22–98 years). Surgery was not performed in 128 women (22.7%) for various reasons, including stage IV or inoperable disease in 77, patient age or concomitant medical disease or senility in 40, patient refusal or death in 11, or unstated reasons in 15. The remaining 434 women comprise the study group; their characteristics are shown in Box 2. Most (64.1%) had advanced disease, and older women (aged over 50 years) were more likely to present with advanced-stage disease than younger women (62.9% [214/340] v 46.8% [44/94]; $P < 0.001$). A quarter lived in rural areas, defined by postcodes outside the Melbourne Statistical Division and the City of Greater Geelong.

Preoperative investigations

Information on preoperative investigations was available for all 434 patients, and included chest x-ray in 39.6% (172), computed tomography (CT) scan in 45.6% (198), ultrasound in 58.5% (254), serum carcinoma antigen (CA)-125 in 58.5% (254); only 35.7% (155) had both a preoperative ultrasound and a CA-125 assay.

Surgical factors

Box 3 shows that primary surgery was performed by general gynaecologists in 156 women (35.9%), gynaecological oncologists in 205 (47.2%), general surgeons in 65 (15.0%) and unspecified specialists in 8 (1.8%). Women aged over 50 years or living in rural areas were more likely to be operated on by general surgeons. In contrast, women with early-stage disease (stages I and II) more commonly had their surgery performed by general gynaecologists than gynaecological oncologists or general surgeons (50.7% [79/156] v 29.3% [60/205] v 24.6% [16/65], respectively; $P < 0.0001$).

When comparing factors related to surgical technique, most women (83.2% [361]) had a vertical incision at surgery.

Only one in three (34.3% [149/434]) surgically treated women had adequate surgery. A quarter with apparent early-stage disease (26.9% [42/156]) had adequate staging surgery, most commonly because of failure to perform pelvic or para-aortic lymphadenectomy; this was performed in only 39.7% (62/156). Gynaecological oncologists were more likely to complete adequate surgery,

compared with general gynaecologists or general surgeons. Box 3 shows this comparison for early-stage disease; overall figures were 52% (105/202) for gynaecological oncologists, 21.3% (35/164) for general gynaecologists and 13.3% (8/60) for general surgeons.

Additional therapy

In general, women were considered eligible for postoperative chemotherapy if they had stage Ic to IV disease, and in stage Ia and Ib disease if tumours were poorly differentiated, showed clear cell morphology or were densely adherent (Box 1). Of the 373 women considered eligible, 323 (86.6%) received postoperative chemotherapy. The reasons provided for those who did not receive chemotherapy included not relevant (26), contraindicated (6), refused (8) and unspecified (10). Five of 21 who were not considered eligible for chemotherapy actually received it. For 13 of the remaining 40 who received chemotherapy, eligibility for chemotherapy could not be determined because of inadequate information (stage unknown [10] and grade unknown [30]).

Of the 373 patients eligible for chemotherapy, 82.6% (308) received a platinum-based regimen such as carboplatin or cisplatin alone or in combination with cyclophosphamide or paclitaxel. Carboplatin or cisplatin was given alone in 14.2% (53); the remaining women received a combination regimen. Only 4.3% (16) received a platinum–taxane combination. Other agents given first-line included chlorambucil (6), etoposide (3), anthracyclines (4), 5-fluorouracil (1) and gemcitibine (1).

Hormone-receptor (oestrogen and/or progesterone) status was measured in 19.4% (84) and hormone therapy (tamoxifen) prescribed in 7.1% (31) in addition to chemotherapy as part of a multicentre randomised phase III trial. Nine patients (2.1%) received radiotherapy, and two had synchronous rectal and cervical cancers warranting radiotherapy.

Prognostic factors and survival

The overall five-year relative survival for women with epithelial ovarian cancer was 46% for those who had primary

2: Patient characteristics and crude survival for women with epithelial ovarian cancer who had surgery as primary treatment

	Number of cases	% Surviving 5 years
All patients	434	31
Age (years)		
< 50	94 (21.7%)	47
50-64	136 (31.3%)	38
65-74	134 (30.9%)	23
75 +	70 (16.1%)	14
Stage		
I	112 (25.8%)	68
II	44 (10.1%)	56
III	216 (49.8%)	19
IV	42 (9.7%)	5
Unknown	20 (4.6%)	6
Morphology		
Serous adenocarcinoma	239 (55.1%)	38
Mucinous adenocarcinoma	65 (15.0%)	71
Endometrioid adenocarcinoma	43 (9.9%)	71
Clear cell adenocarcinoma	21 (4.8%)	70
Adenocarcinoma, unspecified	54 (12.4%)	24
Adenosquamous carcinoma	2 (0.5%)	25
Squamous cell carcinoma	1 (0.2%)	25
Transitional cell carcinoma	1 (0.2%)	25
Undifferentiated/anaplastic carcinoma	8 (1.8%)	25
Tumour grade		
Well differentiated	33 (7.6%)	54
Moderate	70 (16.1%)	29
Poor/undifferentiated	149 (34.3%)	17
Unknown	182 (41.9%)	40
Residence		
Rural	112 (25.8%)	32
Urban	322 (74.2%)	31
Type of specialist		
General gynaecologist	156 (35.9%)	41
Gynaecological oncologist	205 (47.2%)	31
Surgeon/other	65 (15.0%)	12
Unknown	8 (1.8%)	17
Chemotherapy		
No*	93 (21.4%)	48
Yes	341 (78.6%)	27
Radiotherapy		
No*	425 (97.9%)	31
Yes	9 (2.1%)	33
Tamoxifen therapy		
No*	403 (92.9%)	31
Yes	31 (7.1%)	37

*11 women died in the postoperative period and were not considered for further treatment.

surgery and 5% for those who did not have surgery. Multivariate analysis of the surgically treated cases confirmed age, stage, tumour grade and clinical ascites to be independent prognostic factors. The risk of death increased significantly with increasing age, later stage at diagnosis, poorer histological differentiation and the presence of ascites. Histological type, chemotherapy, hormone therapy, treating specialist and treating hospital did not influence survival.

Box 4 shows that when analysing early-stage disease separately, a poorer histological grade, surgery performed by a general surgeon and inadequate staging surgery were associated with a worse outcome. Further, in advanced disease, the absence of ascites and use of hormonal therapy were associated with a better outcome, while chemotherapy also improved the outcome but was of marginal significance. The treating specialist, residual disease and tumour grade were not found to be significant predictors for survival.

3: Patient characteristics, by speciality of treating surgeon

	Obstetrician gynaecologist	Gynaecological oncologist	General surgeon	Unknown	*P*
Total	156	205	65	8	
Age					0.005
< 50 years	38 (24.4%)	50 (24.4%)	4 (6.2%)	2	
> 50 years	118 (75.6%)	155 (75.6%)	61 (93.8%)	6	
Stage					< 0.001
I	55 (35.3%)	45 (22%)	11 (16.9%)	1	
II	24 (15.4%)	15 (7.3%)	5 (7.7%)	0	
III	51 (32.7%)	126 (61.5%)	33 (50.8%)	6	
IV	14 (9%)	16 (7.8%)	11 (16.9%)	1	
Unknown	12 (7.7%)	3 (1.5%)	5 (7.7%)	0	
Residence					0.041
Rural	37 (23.7%)	48 (23.4%)	25 (38.5%)	2	
Urban	119 (76.3%)	157 (76.6%)	40 (61.5%)	6	
Residual disease (late stage only)	65	142	44	7	< 0.001
< 2 cm	23 (35.4%)	77 (54.2%)	8 (18.2%)	2	
> 2 cm	18 (27.7%)	28 (19.7%)	11 (25%)	1	
Unknown	24 (36.9%)	37 (26%)	25 (56.8%)	4	
Staging surgery (early stage only)	79	60	16	1	< 0.001
Adequate	12 (15.2%)	28 (46.7%)	0	1	
Inadequate	67 (84.8%)	32 (53.3%)	16 (100%)	1	
Type of incision					< 0.001
Vertical	121 (77.6%)	185 (90.2%)	53 (81.5%)	2	
Pfannenstiel	21 (13.5%)	1 (0.5%)	5 (7.7%)	0	
Other	1 (0.6%)	2 (1%)	0 (4.5%)	1	
Unknown	13 (8.3%)	17 (8.3%)	7 (10.8%)	5	

P values are for χ^2 tests to determine significance of associations between treating specialist and patient characteristics. Unknown doctor group not included in χ^2 tests.

DISCUSSION

Despite the limitations with a retrospective study, including incomplete data because of failure to report cases, three important deficiencies in management have been identified:

- the infrequent use of preoperative CA-125 assay, pelvic ultrasound and chest x-ray (required for accurate staging);
- the low proportion of women who had adequate staging surgery in apparent early-stage disease; and
- the relatively low proportion who had adequate cytoreductive or debulking surgery in advanced disease

Preoperative workup

Numerous prospective studies have evaluated the role of preoperative ultrasound and CA-125 levels over 35 IU/mL[8] and have found the sensitivity and specificity of these tests to be comparable (62%–85% and 72%–95%, respectively). However, three studies (including one retrospective study) have combined the results, with or without age, to develop a risk score that improves the negative predictive value of the tests.[8-11] Ultrasound in combination with CA-125 assay is recommended for all women with an adnexal mass so that appropriate referral can be made before operation. Only 35.7% of women in our survey had both an ultrasound and a CA-125 assay.

Staging surgery in early-stage disease

The importance of surgical stage as an independent prognostic factor emphasises the value of adequate surgery where disease is apparently confined either to the ovary or pelvis. One study has shown the importance of a vertical incision at surgery in a retrospective study of 291 women with ovarian cancer, as women were more likely to be incompletely evaluated intraoperatively if a transverse incision was performed.[12] Eighty per cent of patients in our survey had a vertical incision.

Internationally accepted standard practice for adequate staging surgery has been described in the report of the National Institutes of Health (NIH) Consensus Conference,[5] which calls for peritoneal washings and sampling of pelvic and para-aortic nodes, as well as omentectomy and biopsy of suspicious areas. In our study, only one in four women with apparent early-stage disease received adequate surgery, most commonly because pelvic and para-aortic lymph node samples were not taken. Although controversy exists about the therapeutic role of pelvic lymphadenectomy, most studies have shown that

lymph nodes can give positive results when disease is clinically confined to the ovary,[13] indicating use of adjuvant therapy with cytotoxic agents. Although no randomised prospective studies have examined survival benefit, one large retrospective, population-based study suggested the outcome for early-stage disease was not affected by surgical staging.[14] By contrast, our study did show staging to be associated with improved survival when tumours were adequately staged.

Gynaecological oncologists were more likely than general gynaecologists and general surgeons to complete adequate staging surgery. One study also showed that gynaecological oncologists complied best with accepted optimal practice,[10] with 97%, 52% and 35% of women having adequate intraoperative evaluation when operated by gynaecological oncologists, general gynaecologists and general surgeons, respectively, in United States university hospitals. However, "adequate surgery" was not defined and 17% of the study population had borderline tumours. A retrospective study of 533 cases of ovarian cancer diagnosed at the West of Scotland Cancer Surveillance Unit not only demonstrated that "adequate surgery" was more likely to be completed by gynaecologists than general surgeons, but also that survival was better.[15] This finding is supported by our study in women with early-stage disease, but such a survival difference may be explained by "stage migration", where failure to complete "adequate surgery" may result in underestimation of some patients' tumour stage, thereby giving the appearance that they had worse results. A US cohort study showed that 31% of early-stage disease was upstaged to stage III if re-operated after referral to one of four Ovarian Cancer Study Group participating institutions.[16]

4: Multivariate relative survival analysis for prognostic factors

Predictor	*P* for contribution to model	Relative risk	95% CI
Early-stage disease (n = 156)*			
Tumour grade	0.0015		
Well/moderately differentiated		1.00	
Poorly/undifferentiated		8.37	(1.86–37.68)
Grade unknown		2.84	(0.61–13.13)
Treating specialist performing surgery	0.039		
Obstetrician and gynaecologist		1.00	
Gynaecologist oncologist		1.58	(0.60–4.17)
General surgeon/other		3.57	(1.41–9.02)
Minimum adequate staging surgery	0.035		
Not done		1.00	
Done		0.26	(0.06–1.14)
Advanced disease (n = 251)†			
Clinical ascites	0.0032		
No		1.00	
Yes		1.58	(1.16–2.15)
Tamoxifen therapy	0.011		
No		1.00	
Yes		0.52	(0.30–0.90)
Stage	0.016		
III		1.00	
IV		1.65	(1.12–2.44)
Chemotherapy	0.054		
No		1.00	
Yes		0.51	(0.27–0.96)
Age group	0.057		
<50 years		1.00	
50–64 years		1.14	(0.73–1.77)
65–74 years		1.23	(0.79–1.91)
75+ years		2.15	(1.24–3.72)

*None of the variables stage, morphology, age group, chemotherapy, urban/rural and hospital were significant in the multivariate model after controlling for the effects of grade, treating specialist and minimum adequate staging surgery.

†None of the variables morphology, tumour grade, type of surgeon, radiotherapy, residual disease, urban/rural residence or hospital were significant in the multivariate model after controlling for the effects of ascites, tamoxifen therapy, stage, chemotherapy and age group.

Cytoreductive or debulking surgery in advanced disease

In late-stage disease the NIH Consensus Conference recommended aggressive efforts at maximal cytoreduction.[5] The aim of cytoreduction is to reduce tumour bulk, because small residual tumours theoretically have better perfusion and a higher growth rate, improving diffusion and efficacy of chemotherapeutic agents[17] in addition to providing symptomatic relief from large, compressive masses. Many retrospective studies, including a meta-analysis of 58 reports, have shown residual disease with tumours less than 2 cm to be associated with a survival benefit.[18] Further, a meta-analysis of four randomised trials of platinum-based chemotherapy showed residual tumour size to be a major determinant of survival.[19] We were unable to confirm optimal debulking surgery to be a significant predictor of survival in women with advanced disease, but this may be because of the large proportion of cases in our study (30%) in which residual disease was not documented. In our study, gynaecological oncologists were more likely to perform optimal debulking surgery. However, the proportion of tumours optimally resected was relatively low, even when surgery was performed by gynaecological oncologists. A retrospective series of 263

cases not only showed that gynaecological oncologists were more likely to perform optimal cytoreductive surgery (defined by residual disease less than 1 cm) in late-stage disease, but also that there was an associated survival advantage in their cohort.[20] We were unable to confirm this improvement in survival, again possibly because of the 30% of cases for which residual disease status was unknown.

Chemotherapy

Chemotherapy is recommended for women with high-risk early-stage and advanced-stage disease after surgery, provided there is no contraindication.[5] Current standard practice is to administer combination chemotherapy consisting of platinum (cisplatin or carboplatin) and a taxane (docetaxel or paclitaxel).[5,21-23] The chemotherapeutic regimens administered in this cohort of women reflected the standard practice of the study time period, which was to use platinum, most commonly alone or in combination with cyclophosphamide. Taxanes became available only in the latter part of the study.

We found an improvement in outcome in women with advanced disease who received tamoxifen. Tamoxifen has been used for relapsed ovarian cancer, as there is some evidence from observational studies that it may produce a response in a modest proportion of women with relapsed ovarian cancer.[24] The results of a local randomised trial are awaited.

CONCLUSIONS

Despite the inherent limitations of a descriptive, retrospective survey, this study highlights some worthwhile issues in the management of ovarian cancer. For optimal care, a preoperative CA-125 assay, chest x-ray and pelvic ultrasound should be performed in women with a pelvic mass, and early referral to a multidisciplinary unit for definitive surgery is advised. Every effort should be made to adequately stage or debulk the tumour. Women with high-risk early-stage and advanced disease should be considered for platinum-based chemotherapy.

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