Pergamon

European Journal of Cancer, Vol. 33, No. 11, pp. 1835–1840, 1997

Printed in Great Britain
0959-8049/97 $17.00+0.00

PII: S0959-8049(97)00192-5

Original Paper

Management and Survival of Ovarian Cancer Patients in South East England

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The aim of this study was to audit the effect of adherence to regionally developed guidelines on survival in women with ovarian cancer. A prospective audit of 118 newly diagnosed cases of ovarian cancer in seven district health authorities of South East Thames, U.K. was undertaken. Appropriateness of clinical investigation and management and survival by type of hospital were examined: 118 incident cases were registered in 1991 for the audit. The mean age of the women was 61.29 years (S.D. 14.24) (range 27–92). 25 (21%) were stage I, 15 (13%) stage II, 77 (66%) stage III/IV. 62 (53%) women had the appropriate pre-operative investigations and 75 (64%) were staged in the notes. Management took place in hospitals treating as few as 1 case a year. Overall, 47 (43%) women were appropriately managed which was influenced by type of hospital of surgery (19 (66%) teaching, 20 (45%) non-teaching with oncology support, 8 (28%) non-teaching (P=0.02)). 64 women (54% died by 1 June 1994) (mean follow-up 2.1 years) (minimum 2.41 years, maximum 3.41 years). In multiple regression analysis, death was significantly more likely in women who had been inappropriately managed, those with more advanced disease and those with postoperative complications. This audit indicates that despite the development of guidelines, investigation and management of ovarian cancer varied considerably between hospitals. Management of this cancer of intermediate incidence occurs in hospitals managing as few as 1 case per year. Pre-operative and operative management was inappropriate for the majority of women and this significantly influenced survival. These data have implications for the purchasing of cancer services for this disease. © **1997 Elsevier Science Ltd.**

Keywords: ovarian cancer, treatment, audit, outcome
Eur J Cancer, Vol. 33, No. 11, pp. 1835–1840, 1997

INTRODUCTION

OVARIAN CANCER is the fourth most common cause of death from cancer amongst females, with an overall 5-year relative survival of just under 30% [1]. There is no evidence that current screening modalities such as transvaginal ultrasound scanning and serum CA-125 measurement are effective at reducing the incidence of the disease [2]. As with much of surgical oncology the evidence of effectiveness of various procedures is based on consensus and case series results rather than randomised controlled trials [2, 3]. There appears to be agreement that the management of early stage disease requires surgery alone and advanced disease requires surgery plus adjuvant chemo and/or radiotherapy [2–4].

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Received 3 Dec. 1996; revised 26 Mar. 1997; accepted 4 Apr. 1997.

In the South East Thames Regional Health Authority (SETRHA), a multidisciplinary group drew up consensus guidelines for the management of cervical, ovarian and endometrial cancers. This study reports on the appropriateness of management of ovarian cancers over a 1 year period, as judged by these guidelines, and its possible effect on survival.

PATIENTS AND METHODS

The 15 districts of SETRHA were ranked according to their standardised mortality ratio (SMR) for cervical cancer in women aged under 65 years (as all gynaecological cancers were being audited and the SMR for cervical cancer was routinely available) and alternate districts from the highest SMR district downwards were selected for the audit. All gynaecological units in these seven districts, two inner London (IL), one outer London (OL) and four rural (RUR), agreed to

participate in the study. Guidelines for the investigation and management of ovarian cancer were developed by a multidisciplinary group and distributed in 1990, together with the audit protocol, to each gynaecologist, medical oncologist and radiotherapist in the participating units [5]. Each unit (4 IL, 3 OL, 16 RUR) was visited by the authors (CW, KSR) and regional meetings were held before and during the audit. All units agreed to the guidelines.

Registration of cases

Ascertainment of all incident cases of ovarian cancer in the study districts between 1 January 1991 and 31 December 1991 was undertaken by two research associates during 1991–1992. Methods and sources of ascertainment have been described elsewhere, with maximum ascertainment being achieved by including sources such as operating theatres, pathology laboratories and the Thames Cancer Registry [5]. Although data were collected on all cases treated in the study units, the audit is restricted to patients resident in and treated in the sampled districts of SETRHA where the guidelines had been agreed.

Data collection

Demographic data including age and health district of residence (based on postcode) were recorded. The pre-operative investigations agreed by the clinicians in the study hospital as essential for good practice in the general management of women with ovarian cancer were noted (full blood count, urea and electrolytes, liver function, chest X-ray) as was the Federation Internationale Gynaecologique Obstetrique (FIGO) stage [6]. During the period of the study, serum CA-125 was not a routine investigation. If there was no stage recorded in the notes, independent staging was performed by a gynaecological oncologist (KSR), using the recorded clinical information. In all cases where staging was mentioned, this was agreed by KSR based on the evidence in the notes. The presence in the notes of a mention of any comorbidity was noted as this may have an influence on survival, e.g. including medical conditions which were currently being treated (e.g. hypertension, respiratory disease) and conditions which may influence operative procedures (e.g. previous pelvic surgery, inflammatory bowel disease).

Appropriate surgery, as defined in the guidelines, was classified as total abdominal hysterectomy and bilateral salpingo oophorectomy (TAHBSO) along with omentectomy. Unilateral oophorectemy with biopsy of the contralateral ovary and omentectomy was considered appropriate in women wishing to retain their fertility with clinical stage 1 disease. Surgery was recorded and categorised as appropriate or inappropriate according to the guidelines (Table 1). Histopathological details of lymph node involvement were recorded. Morphological classification of the tumour (ICD 9 morphology codes) was recorded. Differentiation of the tumour was classified as well, moderate, poor, undifferentiated or not stated. Postoperative complications were noted, including operative and postoperative haemorrhage (volume>500 ml), clinical infections of any site with positive microbiological reports, intestinal obstruction and deep vein thrombosis/pulmonary embolus. Details of the nature of chemotherapy and the number of courses were recorded.

Details of the date and cause of death as indicated on the death certificate were recorded. A record of whether a woman had died of any cause was validated with Thames Cancer registry records, and data censored on 1 June 1994. Survival time was from the date of diagnosis to death or censoring.

The hospital where patients had received surgery and chemotherapy were classified as teaching (T) (a hospital with a medical school attached), non-teaching with support (NTS) (a district general hospital with radiotherapy and oncology services in the district) or non-teaching (NT) (district general hospital). Of the NTS hospitals, two had radiotherapy and chemotherapy on site with clinical oncology support, and two had support in adjacent hospitals.

The investigations employed in the pre-operative management were classified as appropriate if they were in agreement with the guidelines, and inappropriate otherwise, regardless of the reason. The appropriateness of management was considered specific to each stage (Table 2). For women with

Table 1. Patients' characteristics

		Number of patients (n=118)
Age	Mean ± S.D.	61.29 ± 14.24 years
	Median	63 years
	Range	27–92 years
Histology		
Serous cystadenocarcinoma		39 (33%)
Mucinous cystadenocarcinoma		20 (17%)
Clear cell		5 (4%)
Endometrial		7 (6%)
Other		36 (31%)
Unknown		11 (9%)
Differentiation		
Well		15 (19%)
Moderate		34 (44%)
Poor		29 (37%)
Unknown†		39
Stage		
I		25 (21%)
II		15 (13%)
III/IV		77 (66%)
Unknown*		1
Treatment		
Surgery		117 (99%)
Chemotherapy		79 (67%)
Surgery alone		39 (33%)
Chemotherapy only		1 (1%)
Postoperative complications		
Yes		61 (52%)
No		56 (48%)
Location of treatment		
Surgery		117
	Teaching hospital (T)	31 (26%)
	Non-teaching hospital with support (NTS)	54 (46%)
	Non-teaching hospital without support (NT)	32 (27%)
Chemotherapy		79
	Teaching hospital (T)	27 (34%)
	Non-teaching hospital with support (NTS)	52 (66%)
	Non-teaching hospital without support (NT)	0 (0%)

*One patient was not staged because she did not receive surgery. †Differentiation of the tumour was not stated in the clinical notes of 39 (33%) patients who had surgery.

Table 2. Appropriateness of management by stage

Stage	Appropriately managed	*n*	Inappropriately managed	*n*
I (*n*=25)	TAHBSO + omentectomy or less extensive surgery and omentectomy in women wishing to maintain fertility	7 (28%)	Less extensive surgery or chemotherapy	18 (72%)
II (*n*=15)	TAHBSO + omentectomy plus chemotherapy	8 (53%)	Less extensive surgery or surgery only	7 (47%)
III/IV (*n*=69)	TAHBSO + omentectomy or, if inoperable, chemotherapy then surgery	32 (46%)	Less extensive surgery or no chemotherapy* or no operation after chemotherapy	37 (54%)

* 8 patients had surgery but died within 1 month of the operation and are not included in the analysis.

stage III/IV disease who died within 1 month of surgery, appropriateness could not be assessed and these women were therefore excluded from the analysis.

Statistical methods

Categorical variables were compared between groups using the Pearson's chi-squared (χ^2) test, and continuous variables using analysis of variance or *t*-tests as appropriate. The Cox proportional hazards model was used to examine the factors influencing survival [7]. The variables of interest were: age, district of residence (IL, OL, RUR), comorbidity (yes, no), stage (stage I versus II or ⩾III), histology (adenocarcinoma, other), differentiation (well, moderate, poor, undifferentiated, not known), lymph node involvement (positive, negative, not examined), size of residual tumour (⩽5 cm, >5 cm, unrecorded), appropriateness of treatment (appropriate, not appropriate), appropriateness of investigation (appropriate, not appropriate), complications of surgery (yes, no), type of hospital of surgery (T, NTS, NT), and whether the woman had been pregnant or not. The influence of these variables on survival was analysed using a multiple regression model and backwards stepwise elimination to produce a final model where all variables included were significant at the 10% level. The NTS category of hospital was used as the reference category in the hospital variable.

Logistic regression was used to assess which factors affected women having appropriate investigations, whether stage was mentioned in the notes and the appropriateness of management. For the appropriateness of investigations, the factors considered were age, stage, comorbidity, district of residence and hospital of surgery. Backward stepwise elimination was used as a condition of entry/removal of variables. For whether stage was mentioned in the notes, the factors considered were age, stage, comorbidity, appropriate investigations, district of residence and hospital of surgery. Factors considered for appropriateness of treatment included age, stage, comorbidity, appropriate investigations, whether stage was mentioned in the notes, district of residence and hospital of surgery.

In all models, the *P*=value quoted represents the effect of the variable, not the individual categories of that variable.

RESULTS

A total of 139 incident cases of ovarian cancer were registered over the study period. Of the 139 cases, 118 (85%) were resident in and treated within SETRHA, and it is these patients who are the focus of this audit. Patients' characteristics are shown in Table 1. The mean age was 61.29 years (range 27–92) and there were no significant differences in age between districts of residence (data not shown). Those with more advanced disease were significantly older than those with stage I disease (stage I, mean age 52 ± 18; stage II, 66 ± 13; stage III/IV, 63 ± 12; *P*=0.001). Major comorbidity was present in 28 (24%) of cases.

Treatment modality varied significantly with stage, with 10 (40%) of those with stage I disease given chemotherapy compared with 10 (67%) of stage II and 59 (77%) of stage III/IV (*P*=0.004). 117 patients underwent surgery, and the operating notes mentioned residual tumour size in 55 (47%) cases. Of these, 6 were between 2 and 5 cm, and 49 were larger than 5 cm. 61 (52%) patients had postoperative complications.

Type of hospital

117 patients underwent surgery (Table 2), which took place in 18 different hospitals, treating between 1 and 18 patients over the study period, with a mean (± S.D.) of 7 ± 5.00 and a median of 7 patients. Chemotherapy was given to 79 (67%) of the cases and was carried out in 7 centres. These centres treated between 1 and 27 patients, with a mean of 11 ± 10 and a median of 11 patients. Of all the oncologists, there was only one gynaecological oncologist practising, who worked in a TH. Women who received chemotherapy did so in the same T or NTS hospital in which they had received their surgery, while of those who had undergone surgery in an NT hospital, 18 had chemotherapy in an NTS hospital and 3 in a T hospital.

There was no significant difference in age, comorbidity, tumour differentiation or treatment modality between the patients treated at T, NTS and NT hospitals. There was a significant difference in stage of disease between the types of hospital (Table 3), with the T hospital treating more patients with advanced stage disease (*P*=0.02). There was also a significant difference in postoperative complications between the types of hospital, with 21 (68%) of T cases, 30 (56%) of NTS cases and 10 (31%) of NT cases having complications (*P*=0.01),

Table 3. Stage by type of hospital of surgery

	T (*n*=31)	NTS (*n*=54)	NT (*n*=32)	Total (*n*=117)
Stage I	2 (6%)	10 (19%)	13 (41%)	25 (21%)
Stage II	5 (16%)	7 (13%)	3 (9%)	15 (13%)
Stage III/IV	24 (77%)	37 (69%)	16 (50%)	77 (66%)

χ^2=9.9 on 4 df, *P*=0.02. 1 patient had no surgery.

Table 4. The proportion of women having appropriate investigations, staging mentioned in the notes and appropriate treatment

	All investigations	Not all investigations	Stage in notes	Stage not in notes	Appropriately treated	Inappropriately treated
Number of women	62 (53%)	56 (47%)	75 (64%)	43 (36%)	47 (43%)	62 (57%)
Age (years)						
Mean (S.D.)	65 (11.8)	57 (15.5)	61 (13.9)	61 (15.0)	59 (11.8)	62 (15.6)
Median (range)	66 (27–92)	59 (30–86)	63 (27–89)	63 (30–92)	62 (31–85)	65 (27–89)
Hospital						
T	18 (58%)	13 (42%)	21 (68%)	10 (32%)	19 (66%)	10 (34%)
NTS	26 (46%)	30 (54%)	32 (57%)	24 (43%)	20 (40%)	30 (60%)
NT	18 (60%)	12 (40%)	22 (73%)	8 (27%)	8 (28%)	21 (72%)
Stage						
I	10 (40%)	15 (60%)	15 (60%)	10 (40%)	7 (28%)	18 (72%)
II	9 (60%)	6 (40%)	9 (60%)	6 (40%)	8 (53%)	7 (47%)
III/IV	43 (55%)	35 (45%)	51 (65%)	27 (35%)	32 (46%)	37 (54%)
Comorbidities						
Yes	14 (50%)	14 (50%)	18 (64%)	10 (36%)	8 (35%)	15 (65%)
No	48 (53%)	42 (47%)	57 (63%)	33 (37%)	39 (45%)	47 (55%)
All investigations						
Yes	NA	NA	44 (71%)	18 (29%)	20 (36%)	36 (64%)
No	NA	NA	31 (55%)	25 (45%)	27 (51%)	26 (49%)
Staged						
Yes	NA	NA	NA	NA	32 (44%)	40 (56%)
No	NA	NA	NA	NA	15 (41%)	22 (59%)

reflecting the more advanced and therefore complicated cases seen by the T hospital. There was a significant association between stage of disease and postoperative complication rate, with 7 (28%) of stage I, 9 (60%) of stage II and 45 (58%) of stage III/IV patients having complications (P=0.03).

Appropriate diagnostic investigations

The number of women receiving the appropriate diagnostic investigations is shown in Table 4 with only 63 (53%) receiving all the recommended diagnostic procedures. However, there was no significant difference (univariate) between those who did or did not receive all the investigations for the parameters analysed, except for age, where women who received the appropriate tests were significantly older (P=0.0014). In multiple logistic regression, increasing age was significantly associated with having appropriate investigations (odds ratio (OR) 1.053, 95% confidence interval (CI) 1.02–1.08, P=0.003).

Appropriate treatment/management

The number of women receiving the appropriate treatment is shown in Tables 2 and 4. 7/25 (28%) stage I, 10/15 (67%) stage II and 36/78 (48%) stage III/IV underwent an omentectomy. However, there was no significant difference (univariate) between those who did or did not receive appropriate treatment for the parameters analysed, except for the type of hospital in which the patient underwent surgery, where significantly more women were appropriately treated in a T hospital compared with NTS or NT (P=0.02). There was a significant difference in the number of patients having TAHBSO plus omentectomy, with 21 (68%) of T, 21 (39%) of NTS and 10 (31%) of NT patients having this operation (P=0.008). Of the 7 women under the age of 40 years with stage I disease, 4 had TAHBSO with omentectomy, 2 had unilateral oophorectomy and 1 an ovarian cystectomy. In multiple logistic regression, appropriate treatment was associated with the type of hospital (T, OR=1 (ref); NTS, OR=0.201 95%=CI 0.07–0.61; NT, OR=0.351 95%=CI 0.14–0.91; P=0.0107).

Survival analysis

The last date on which patient status is known was 1 June 1994, at which point 64 (54%) patients had died. The minimum follow-up time was 2.42 years and the maximum possible was 3.41 years. Overall median survival was 931 days (mean 757 ± 406); for the patients who died, median survival was 367 (mean 416 ± 311) and for those still alive, median survival was 1108 days (mean 1085 ± 100).

In the Cox proportional hazards model (Table 5), the risk of death was significantly higher for those inappropriately treated, those with more advanced disease, those with postoperative

Table 5. Cox proportional hazards model for survival of ovarian cancer (stage ⩾II only)

Variable	Hazard ratio	95% CI	P value
Stage I	1.00		<0.0001
Stage II	2.40	0.52, 11.04	
Stage III or IV	14.52	4.32, 48.82	
Appropriately managed	1.00		0.0043
Inappropriately managed	1.48	1.34, 4.78	
No complications of surgery	1.00		0.0004
Complications of surgery	3.13	1.66, 5.90	
Teaching hospital	0.32	0.15, 0.66	
Non-teaching plus support hospital	1.00		0.0067
Non-teaching hospital	0.26	0.12, 0.57	
No pregnancies	1.00		0.035
⩾1 pregnancy	0.51	0.28, 0.95	

complications, those managed in NTS hospitals, and in women who had never been pregnant.

DISCUSSION

This audit compares ovarian cancer management for a population of seven health authorities in England with agreed guidelines. With the advent of the Calman–Hine report on the shaping of cancer services, commissioning agencies require information on which to base decisions on where services are to be located and what packages of care are effective [8]. For ovarian cancer, women of these seven districts are managed in 22 hospitals with surgeons performing, on average, one operation every 2 months. Chemotherapy is given in centres which see between one new case a year and one new case every 2 weeks. These basic observations alone deserve further discussion with rationalisation of existing service provision.

Over the past 5 years consensus documents in the United States and United Kingdom have produced guidelines for the management of ovarian cancer which are broadly in agreement with those produced for the South Thames audit in 1988 [2, 3]. In the current audit, 53% of cases were appropriately investigated which compares with 15% for cervical cancer in the same study districts [5]. With only just over half the women being appropriately investigated, the possibility of understaging and consequent inappropriate subsequent surgery and chemotherapy has to be considered. It appears that older women were more appropriately investigated, perhaps because of increased awareness by the clinician of the possibility of ovarian cancer in this age group.

Only 64% of women had stage mentioned in the notes but this was increased in teaching hospitals where a multidisciplinary approach to management was routine. This may indicate that the clinical oncologists frequently note the stage rather than the surgeon, but this was not studied specifically.

48% of women had an omentectomy and of those with stage I disease only 25% had had an omentectomy, indicating possible understaging. The appropriate management of early stage disease is based on a consensus view and although the evidence of effectiveness for surgical procedures is relatively weak, the evidence for chemotherapy is based on trial evidence [2, 4, 9]. Overall, adherence to the SETRHA guidelines would appear to have had a beneficial effect as survival was significantly improved if appropriate treatment was undertaken. There was significantly less appropriate surgery undertaken in non-teaching hospitals. Similarly, overall management was more often appropriate in teaching hospitals and hospitals managing more cases. Although this phenomenon of teaching hospitals having improved outcomes has been recorded for other cancer sites, e.g. breast and teratoma, the reasons remain largely unexplained.

In the multiple regression model, a factor previously known to reduce survival was confirmed, i.e. stage of disease. An unusual, unexplained finding was that survival was independently associated with whether a woman had ever been pregnant, with a protective effect of having had a pregnancy. Patients inappropriately managed had a 1.48 increased risk of death after confounding factors were controlled for. Management in a non-teaching support hospital appeared to reduce the chances of survival compared to teaching hospitals but management in non-teaching hospitals had a beneficial effect. The hospitals were categorised by hospital of surgery and the effect of the hospital at which chemotherapy was given on survival could not be established with confidence as the numbers in the model were too few. One possible confounding factor is that NT hospitals have a better outcome as they refer patients to NTS and T hospitals for chemotherapy. The numbers involved in the categories are small and caution in interpretation of the data is required.

A study of breast cancer management has shown that survival is improved if care is by a specialist surgeon but the setting in which these surgeons worked, the multidisciplinary nature of the teamwork and whether care was appropriate were not discussed [10]. The same group reported that survival of women with ovarian cancer in Scotland was improved in teaching hospitals but the factors within such settings that could explain the findings were not explored in the first study [11]. A retrospective case note analysis of all cases of ovarian cancer managed in Scotland by the same group in 1987 revealed that patients first seen by a gynaecologist, those operated on by a gynaecologist, those having surgery to debulk the tumour to less than 2 cm postoperatively, those given chemotherapy and those followed up in a joint clinic had improved survival [12]. In the United States, Mayer and associates showed, using univariate analysis, that treatment of ovarian cancer by gynaecological oncologists improved survival compared to non-specialists but again the context in which these observations were noted was not analysed [13]. Similar findings were found in a retrospective note review by Grant and associates [14]. The current study has observed differences in the appropriateness of management of ovarian cancer which have an overall significant effect on survival. It still remains to be elucidated which attributes of a hospital are conducive to adherence to guidelines, and hence appropriate management. Further research into why clinicians decided to manage these cancer cases as they did, rather than as the guidelines outline, is required before services can be developed to improve the appropriateness of cancer care for this group of women.

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Acknowledgements—We would like to thank the health care professionals in the districts who participated in the study, Gill Smith and Vanessa Church for field work, the South East Thames RHA Audit Committee for funding, the Thames Cancer Registry, particularly Heather Bourne, for supplying us with data and advice, and Carole Price for preparation of the manuscript.