Development of an evidence-based algorithm for the management of ovarian cancer

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Summary

Objective: To describe the management of ovarian cancer to be undertaken by a gynaecologist and to describe the highest level of primary research evidence supporting it.

Design: Use of regional guidelines and semi-structured interviews with gynaecological oncologists to devise a flow-chart algorithm for management. Use of an algorithm to identify the key research questions and to define search strategies for primary research, which was assessed using pre-defined criteria for validity.

Main Outcome Measures: Highest level of evidence for each research question based on the design of the valid studies.

Results: Prospective cohort studies (level II-2A) support the algorithm's diagnostic procedures. The evidence for accurate staging is derived from case series data (level II-2B). Preserving the uterus in young women wishing to maintain fertility is supported by prospective cohort studies (level II-2A) and by case series data (level IV) for women with germ cell tumours. Prospective cohort studies (level II-2A) support surgical management with hysterectomy, bilateral oophorectomy and debulking. The evidence for chemotherapy comes from randomised controlled trials (level I), except for germ cell tumours where the evidence was from case series data (level IV).

Conclusions: The management of ovarian cancer and the level of evidence supporting it can be described using a flow-chart algorithm. Evaluations of whether this presentation helps consultants follow guidelines are required.

Key words: Ovarian cancer; Clinical algorithm; Evidence-based medicine.

Introduction

Five-year survival for ovarian cancer in England lies below the European average [1]. In the UK, Wolfe *et al.*, distributed text guidelines for the management of ovarian cancer to all gynaecologists in the South East of England [2]. Adherence to the steps recommended for diagnosis, staging and initial surgical management improved 2-year survival by 20% but only 40% of patients received such care.

The guidelines distributed by Wolfe *et al.* could be improved by showing the evidence supporting each recommendation. Evidence-based medicine is the explicit and judicious use of the best current evidence in making decisions about the care of individual patients [3]. It seeks to convert clinically important information about practice into answerable questions, to track down the best evidence with which to answer them, to critically appraise the evidence and to apply the results. A guideline that is explicit about its evidence base could be a more persuasive means of changing clinician behaviour than one that is not.

The guidelines were presented in the form of a bulky text document. Flow-charts have been shown to be better than plain text guidelines at imparting hospital policy to a variety of clinical and clerical staff [4, 5]. Clinical algorithms presented as flow charts, have been evaluated as successful aids in diagnosis [6], determination of prognosis [7, 8], and therapy [9].

This paper describes the development of a flow-charted clinical algorithm to describe the gynaecological management of ovarian cancer to general gynaecologists based on local guidelines. Clinical questions were identified about the key steps of the algorithm and the highest level of evidence sought from primary research, in favour of the selected clinical actions. By setting a standard for care in this way, audits may be used to investigate whether current care matches the guidelines thereby beginning the process of improving care.

Methods

The clinical algorithm was created in discussion with gynaecological oncologists by listing the clinical actions and decisions they took for cases of ovarian cancer based on existing guidelines. Since the evaluation of every pathway through the algorithm would not be feasible, key clinical questions were also identified in these discussions.

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The key clinical questions were converted into search strategies by defining the patients, the intervention, a comparison and an outcome [3]. The outcome considered important for diagnosis was scheduling the woman for laparotomy; for staging, surgery and referral for chemotherapy the selected measure was survival. Whilst investigations to exclude bowel cancer are important in the management of pelvic masses associated with bowel symptoms, the validation of this part of the algorithm is not central to the determination of levels of evidence for the management of ovarian cancer, so this was not the subject of literature review.

For each question, a search was designed to find English language primary research published during the period 1988 to 1998 and indexed on MEDLINE. All strategies used the subject heading: "ovarian neoplasms" as well as the text: "ovarian cancer" to identify disease specific articles.

Literature for questions about diagnosis was identified using the subject headings: "ultrasonography", "CA125 antigen", "biopsy, needle" and "laparoscopy" and the text words: "ultrasound", "CA125", "aspiration" and "cytology". These were combined with a strategy to find research for diagnostic problems [10]. Research into the use of diagnostic tests for screening was rejected in favour of studies of hospital inpatients with a histological diagnosis as a gold standard because these were considered the best reflection of the circumstances in which the algorithm would be used.

The subject headings, used to identify papers for the questions on staging and surgical management, were "neoplasm staging", "neoplasms, germ cell and embryonal" and "hysterectomy" and the text words were: "FIGO", "stage", "appropriate", "tah", "bso", "debulking" and "residual". These were incorporated into strategies to find studies addressing prognosis and therapy problems [11, 12]. The subject headings, used to identify the papers on postoperative management, were "antineoplastic agents" and "chemotherapy, adjuvant". These were incorporated into strategies for finding studies to address therapy problems [12].

The validity of the full text of relevant papers, identified by reading the title and abstract, was assessed using criteria proposed by Sackett *et al.* [3]. Valid articles were given a level of evidence using a scheme similar to that proposed by the National Health Service Centre for Reviews and Dissemination (Table 1) [13]. The original scheme placed the comparison of a prospectively recruited case series with historical controls at the same level as concurrently controlled cohort studies and had no place for data from uncontrolled case series or audits. We moved the former to level III evidence and the latter to level IV evidence. The highest level of evidence in support of the algorithm is reported.

Table 1. — *A Hierarchy of Evidence [13].*

Level of evidence	Research design
I	Randomised controlled trials
II-1	Non-randomised controlled trials
II-2A	Prospective concurrently controlled cohort studies
II-2B	Retrospective concurrently controlled cohort studies
II-3	Case-control studies
III	Comparison of case series with and without intervention at different times or places, showing a large difference
IV	Results from single case series/audits or the opinions of respected experts

Results

Figures 1, 2 and 3 show the flow-charts of the final algorithm. Figure 4 provides a key to the symbols used.

Diagnosis

The questions asked about diagnosis were:

1) "What is the false negative rate of pelvic examination, ultrasound and serum cancer antigen 125 (CA125) for patients referred to a gynaecologist?"

2) "What is the false negative rate of cyst aspiration for patients with a unilocular, non-echogenic cyst, persisting for more than three months and a negative CA125?".

Two studies showed that following ultrasound and CA125, the false negative rate was zero. One study reported the histological diagnosis of 53 patients who had a negative pelvic examination, ultrasound and a normal CA125 [14]. The other reported the diagnosis of 102 women who had a negative ultrasound and a normal CA125 [15]. Both of these studies validate the algorithm only for postmenopausal women scheduled for laparotomy. Neither study reported whether the histologist was blind to the previous test results. The studies were graded level II-2A.

Two studies showed that cyst aspiration has a low false negative rate. One determined the results of laparoscopic cyst aspiration after clinical examination and ultrasonography. Of 51 patients, aged 12-89, with a subsequent histological diagnosis, none with a negative clinical examination, ultrasound and cyst aspirate cytology had a malignancy [16]. In the other, a cohort of women aged 17-90 years were investigated by fine-needle biopsy and fine-needle aspiration if the lesion was solid or solid and cystic on ultrasound prior to laparotomy. Of 57 aspirates reported as benign, two were malignant on subsequent independent histology. Among the inadequate samples (4/91) one was found to be malignant [17]. No studies reported the use of cyst aspiration among women with unilocular cysts persisting for more than three months with a normal CA125. The reported studies were graded II-2A.

Staging

The question asked about staging was: "Does incorrect FIGO (International Federation of Gynecology and Obstetrics) staging for ovarian cancer affect survival?" [18].

A study of 94 restrospectively identified cases of Stage I-IIa epithelial ovarian cancer showed in a univariate analysis that survival was 20% higher for accurately staged patients. Multivariate analysis allowing for a DNA index, DNA ploidy stage, histological type, grade, and volume percentage epithelium showed that accurate staging was not an independent predictor of survival [19]. A second study retrospectively reviewed the management of 47 Stage I or II patients. Those managed by gynaeco-

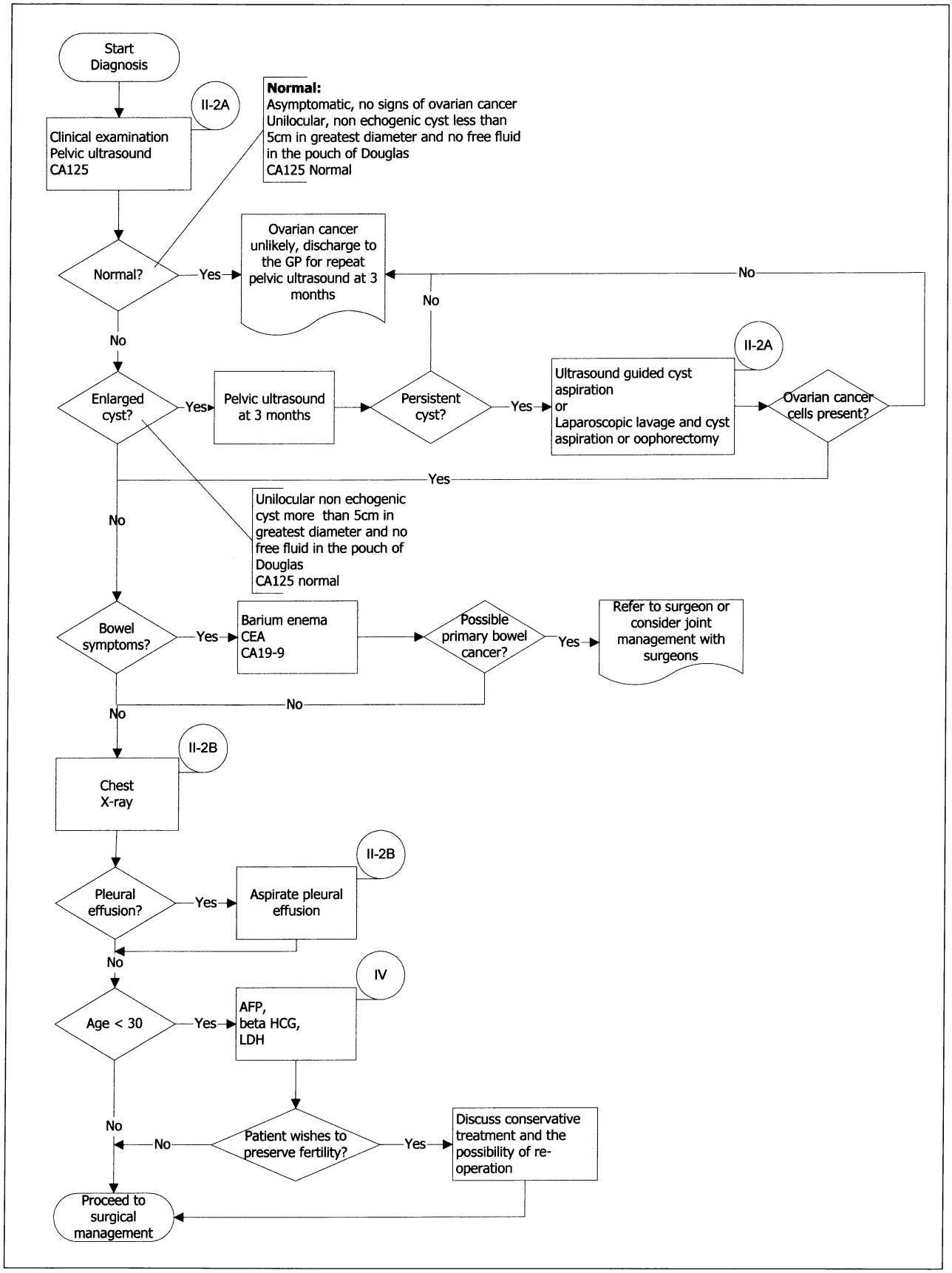

Figure 1. — Preoperative management of primary ovarian cancer.

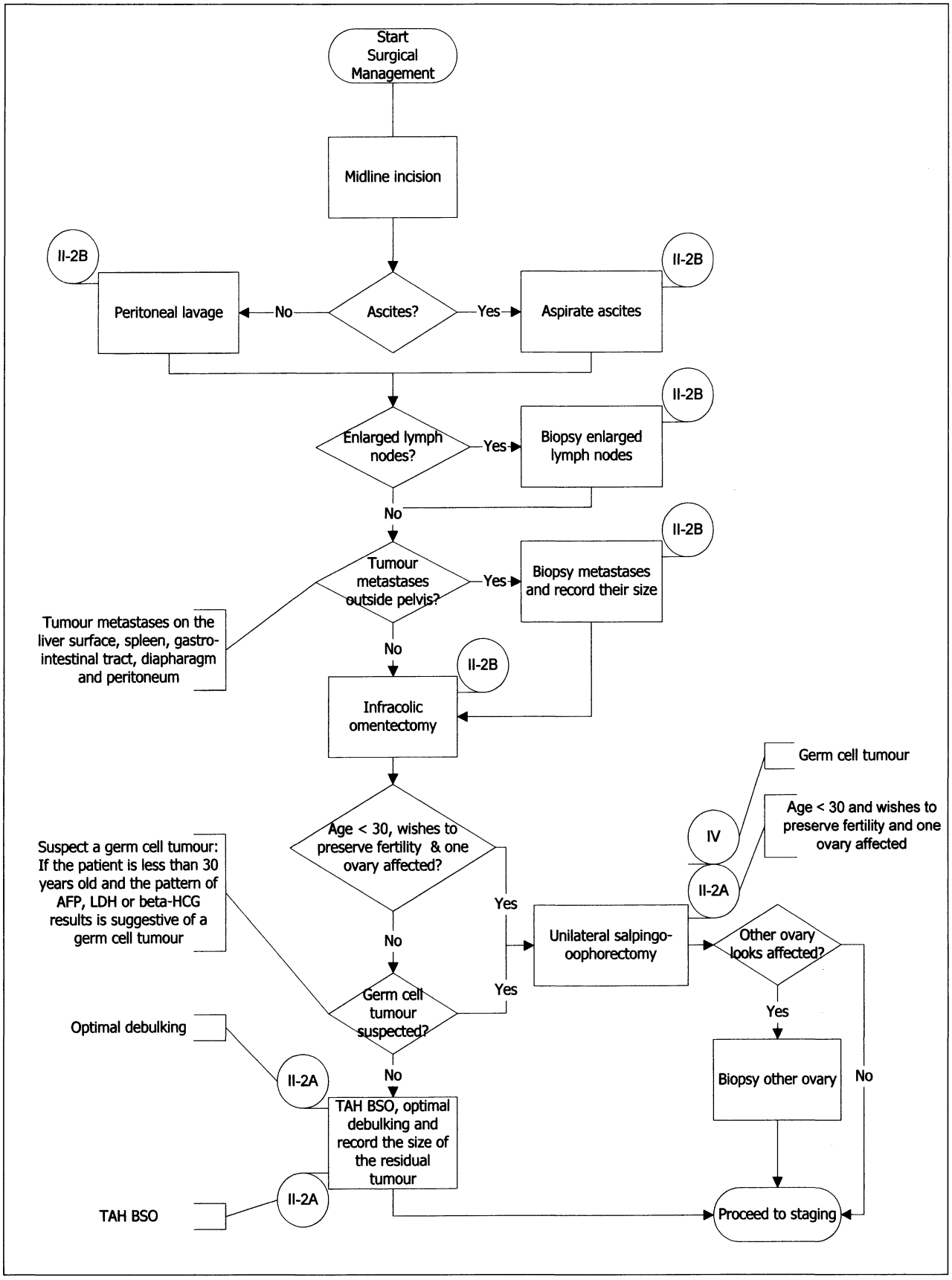

Figure 2. — Surgical management of primary ovarian cancer.

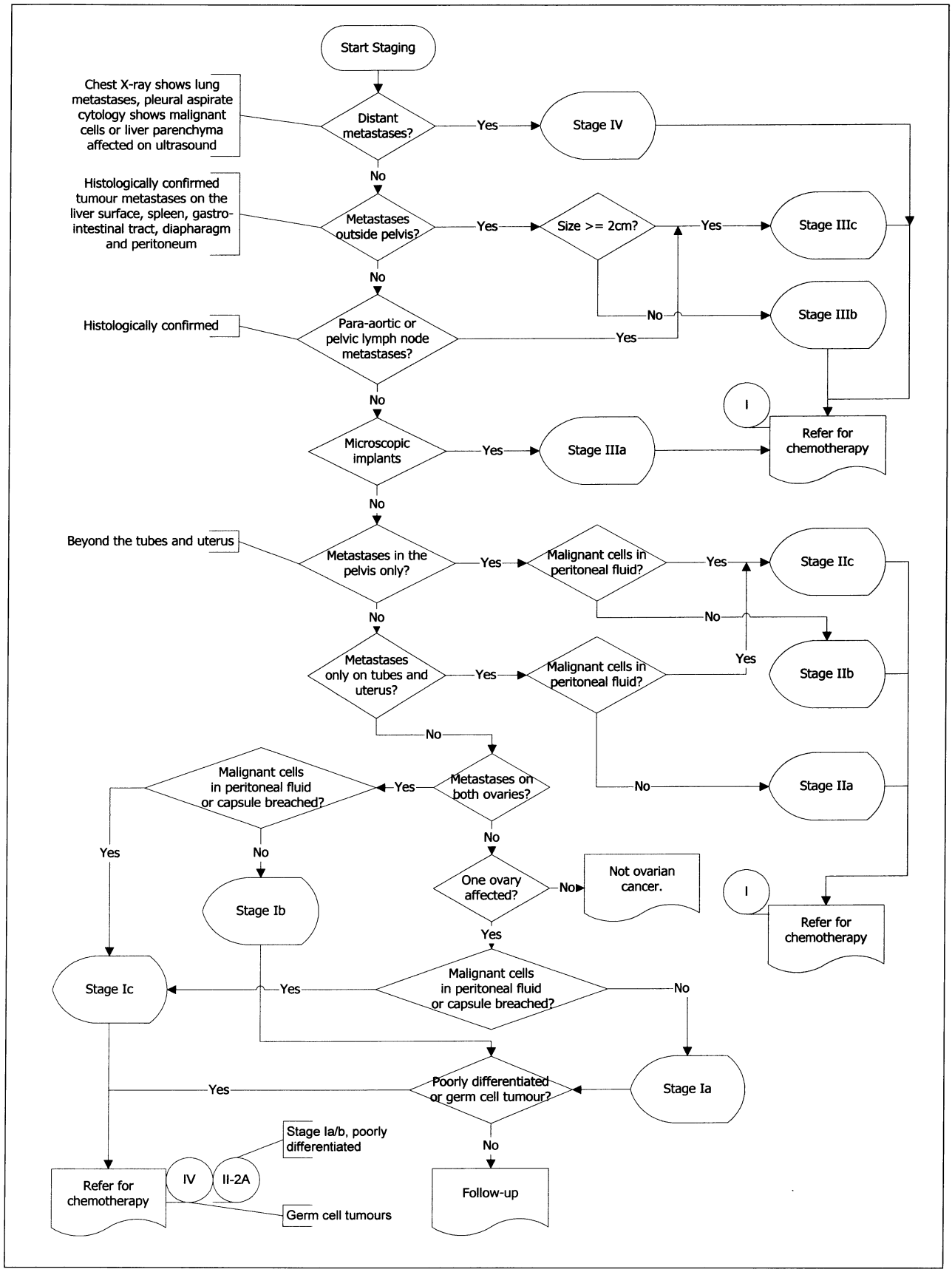

Figure 3. — Staging of primary ovarian cancer.

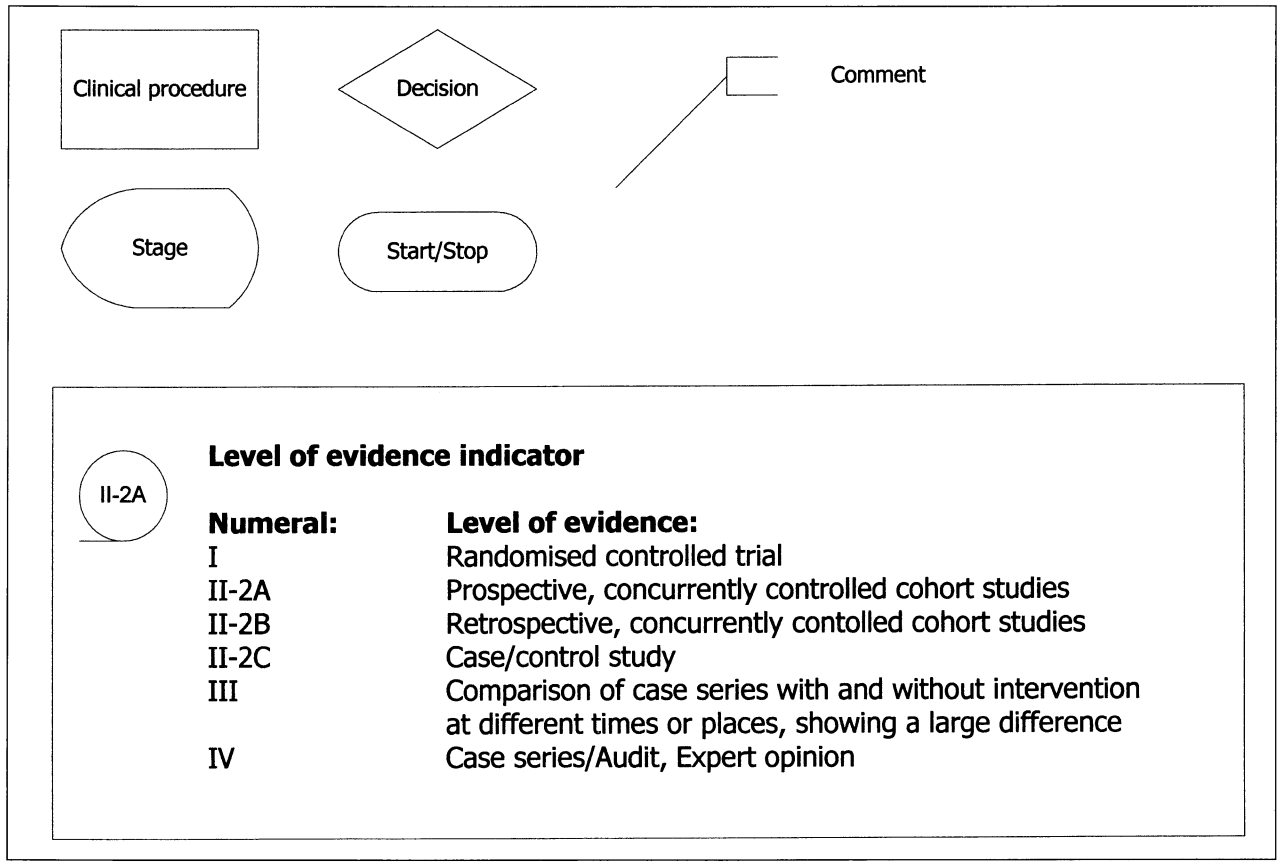

Figure 4. — Key to the flow-chart symbols used in the algorithm.

logic oncologists had an 83% survival versus 59% for gynaecologists or general surgeons, the reported stage and grade being equal. The staging procedures omitted in the latter group were omentectomy, lymph node sampling and peritoneal biopsy [20]. These studies were graded II-2B.

Surgical management

The questions asked about surgical management were:

1) "Does a unilateral salpingo-oophorectomy and preservation of the uterus (conservative surgery) adversely affect survival for patients with Stage Ia ovarian cancer?"

2) "Does failing to perform a TAH BSO (total abdominal hysterectomy and bilateral salpingo-oophorectomy) adversely affect survival?".

3) "Does removing tumour volume (debulking) benefit survival in patients with later stage disease?".

Survival is unaffected by the use of conservative surgery. In a prospective study of 99 women under 40, with accurately determined Stage I ovarian cancer, 56 women (57%) underwent conservative surgery. In a multivariate analysis allowing for age, grade and sub-stage, conservative surgery resulted in no different survival or disease-free survival during a follow-up period of between three and 15 years [21]. The study was graded II-2A.

No papers addressed the second question about TAH BSO directly. Data were reported from a randomised controlled trial involving 301 patients with Stages IIb to IV epithelial ovarian cancer which compared sequential versus alternating chemotherapy and found no difference. Performing an abdominal hysterectomy, bilateral oophorectomy and omentectomy as opposed to alternative procedures (types not described) increased the risk of tumour being found at second-look surgery, allowing for residual tumour size, stage, leukocyte count and platelet count [22]. The study was graded II-2A.

No studies compared a policy of debulking with a policy of not debulking. A series of 91 Stage III and IV epithelial ovarian cancer patients underwent an abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy with attempted additional resection of tumour to achieve the most radical procedure possible. Postoperatively the patients all received cisplatin-based chemotherapy. Multivariate modelling, allowing for stage, age, histological type, chemotherapy dose and response to treatment at second-look laparotomy, showed that no residual disease predicted better survival [23]. The study was graded II-2A.

This study is typical of many that assess residual disease status by various means of measurement ranging from: maximum width less than or greater than 1 cm [24], maximum width less or greater than 2 cm and number of lesions, [25] to measures of the width and position of lesions [26]. All were graded II-2A/B.

Postoperative management

The questions asked about postoperative management were:

1) "Does platin-based chemotherapy improve survival for patients with Stage Ic-IV ovarian cancer?"

2) "Should women with Stage Ia or Ib disease and a poorly differentiated tumour have chemotherapy?"

Platin-based chemotherapy seems to improve survival. A randomised controlled trial comparing cisplatin, doxorubicin and melphalan with the use of the latter two drugs only involved 295 patients with Stage III and IV epithelial ovarian cancer. This showed in a multivariate analysis allowing for residual tumour, ascites and grade that cisplatin containing chemotherapy improved survival and disease-free survival [27]. A second study reported the long-term follow-up of a randomised controlled trial of 186 patients with Stage III or IV epithelial ovarian cancer comparing the use of a cisplatin containing combination of drugs versus an alternative without cisplatin. Five- and ten-year progression-free survival was 24% and 21% for those prescribed the cisplatin containing chemotherapy compared with 9% and 5% for those receiving the alternative [28]. Neither of the studies attempted to blind the patients or the assessor to the outcome. Both were graded level I.

The evidence regarding whether patients with Stage Ia or Ib ovarian cancer should have chemotherapy is equivocal. A trial of 85 patients with Stage Ia and Ib epithelial ovarian cancer randomised them to receive cisplatin or observation using a concealed list technique. Most patients who relapsed were given cisplatinum containing regimens. On an intention-to-treat basis after complete follow-up, five-year survival and disease-free survival was the same in both groups. A multivariate analysis showed that grade and treatment were the only independent predictors of disease-free survival after allowing for age and histological type [29]. The study was graded level I.

Germ cell tumours

The questions asked were:

1) "What is the sensitivity and specificity of alpha-fetoprotein, beta-human chorionic gonadotrophin and lactate dehydrogenase for germ cell tumours of the ovary for women with an abnormal ultrasound and CA125 both suggesting ovarian cancer?".

2) "Is patient survival adversely affected by management of germ cell tumours using conservative surgery and chemotherapy?"

No evidence could be found assessing the first question regarding the tumour marker question so the evidence is graded level IV because it is the opinion of experts in the field.

Regarding the second question about management, no studies comparing the management proposed by the algorithm to alternatives could be found. Ninety-three patients with Stage I to III germ cell tumours were followed up for between 4 and 90 months after either a unilateral salpingo-oophorectomy with preservation of the uterus (67 patients) or a hysterectomy and bilateral salpingo-oophorectomy. All patients were prescribed bleomycin, etoposide and cisplatin chemotherapy. Eighty-nine patients were continuously free of disease after initial management and two patients were given additional chemotherapy for recurrence [30]. A second study reported a survival rate of 96% after six to 153 months of follow-up of a case series of 129 patients with germ cell tumours of all stages. Of these 108 were treated with unilateral salpingo-oophorectomy and preservation of the uterus. Chemotherapy was administered to all except those with Stage I dysgerminoma [31]. Both studies were graded IV because of the lack of a control group.

Discussion

The clinical algorithm improves on the presentation of existing guidelines [32, 33] because it is compact (3 flowcharts) and describes not only which clinical actions should take place but also the decisions that should follow. In addition the process of development of the algorithm meets the standard that a guideline should be explicit about how the evidence was identified, validated and combined [3].

The search methodology is open to the criticism that by searching only one database, papers providing a higher level of evidence could have been missed. Searches for all relevant papers may be considered as a hierarchy of steps: first search one database, second search multiple databases, third perform manual searches through relevant journals. Each additional step adds to the cost of searching.

The ability of electronic database searches to find relevant papers is dependant on the accuracy of indexing. The searches used to compile the algorithm found many more irrelevant than relevant articles, which meant that correct selection was dependant on the accuracy of the abstract. Neither electronic database searches nor manual search strategies can access data not published due to editorial bias for positive results.

This suggests that performing more database searches will yield fewer and fewer useful articles. It follows that there is a cost/benefit from searching for all relevant articles that account has to be taken of the available resources. The resources available for this study precluded using more intensive searches because of the multitude of clinical questions that were being addressed. The UK National Health Service Executive (NHSE) has published text guidelines for those commissioning gynaecological cancer services [33]. These make recommendations about the management of ovarian cancer based on a series of wide ranging systematic reviews. In no instance did the more extensive searching carried out by Melville *et al.* in compiling the National Health Service Executive's guidance [33], change the recommendation or improve the level of evidence.

Bias in the review of each clinical question was avoided by ensuring that the method of searching for

papers was explicit, that pre-defined criteria for relevance and validity were applied and that papers were selected whether or not they supported the algorithm. The method of ranking research purely on design avoided the subjective element of the original scheme [13] that required a decision about whether research was: "well designed". Instead criteria for validity were applied to each study. The criteria were selected because they were appropriate for clinicians to use in assessing papers [3]. They depend on the publication of all the relevant information to make an assessment. The benefit of the doubt was given to the authors of the paper being reviewed, where relevant data were missing, such as with regard to the method of randomisation.

For situations where randomised trials are inappropriate such as the assessment of diagnostic tests against a gold standard, the maximum attainable level is II-2a – prospective cohort study. Cases such as this and germ-cell tumour management suggest the need to improve the level of evidence scheme by grading evidence separately for each type of research question (diagnosis, treatment, prognosis, etc.) taking account of the best attainable research design.

The NHSE guidance for commissioning gynaecological cancer services in the UK [33] investigated the use of age, morphological and doppler ultrasound and CA125 and concluded that preoperative evaluation of pelvic masses can be used to determine whether women are likely to have ovarian cancer. The algorithm refines this statement by suggesting that women with persistent ovarian cysts and a normal CA125 should be investigated by cyst aspiration. Ultrasound-guided cyst aspiration or a laparoscopic alternative might be unsafe because spillage of malignant cells in the abdomen worsens prognosis. Studies investigating pre- or intraoperative rupture (graded as level II-2A) provide contradictory evidence about the effect on survival [34, 35]. The algorithm seeks to ensure that only patients with a very low probability of malignancy have this procedure so that any potential adverse effects that may exist will be minimised. There was only one instance where no evidence could be found: the use of biochemical tumour markers to indicate the presence of a germ cell tumour. No alternative management was suggested by the literature, so it was decided to class the evidence as level IV – evidence from the opinions of experts.

The algorithms concur with the NHSE guidance that conservative surgery can be offered to women with Stage IA ovarian cancer [33]. The algorithm suggests preoperative counselling and full surgical staging prior to proceeding, if it is clinically apparent that only one ovary is affected.

The case for debulking is dependent on the finding that less residual disease is associated with longer survival and disease-free survival. Heintz *et al.* suggest that the amount of residual disease may be affected by the initial characteristics of the tumour and that the residuum does not have any independent effect on survival [36]. None of the studies read were designed to compare a policy of radical debulking with an alternative procedure. We suggest that such research is required to determine the value of debulking surgery.

Level I evidence supports the use of chemotherapy for advanced (Stages II-IV) ovarian cancer. The selection of an appropriate regime was beyond the scope of the questions asked in this paper. Level II-2A evidence supports the use of chemotherapy for early stage disease with adverse prognostic factors such as malignant ascites or washings, poor differentiation or capsule breach by the tumour, each of which, if present, would result in Stage Ic being assigned. Like the recommendations of the NHSE guidance, the algorithm suggests that gynaecologists should refer all patients with Stage Ic-IV ovarian cancer for the opinion of an expert in chemotherapy for gynaecological tumours [33].

Conclusions

A flow-chart clinical algorithm has been developed, which is supported by varying levels of evidence from the literature, being weakest for gynaecological surgical procedures and strongest for chemotherapy. This compact presentation will allow the clinician to determine which components of his/her practice should change. The next step is to audit patient care when this algorithm is being used to determine if it changes clinician behaviour.

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