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Understanding the problem of inadequately staging early ovarian cancer

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ABSTRACT

Background: Early ovarian cancer patients are often incompletely staged during initial surgery.[1–3] This omission can have serious adverse consequences for the prognosis of patients as the completeness of surgical staging has been identified as an independent prognostic parameter for survival.[4,5] The reasons for the problem of inadequate staging of early ovarian cancer are largely unknown. We have analysed the data of a large randomised trial in early ovarian cancer in which detailed information of the surgical staging procedure was monitored.[5]

Methods: Data of the EORTC Adjuvant ChemoTherapy In Ovarian Neoplasm (ACTION) Trial were used in which 448 early ovarian cancer patients were randomised between postoperative chemotherapy in one arm and observation following surgery in the other. In this trial strict criteria for surgical staging were advised but optimal, complete staging was performed in only 1/3 of patients. Staging characteristics of the incompletely staged patients were analysed and factors that could explain the failure to perform a complete staging were studied.

Results: Sampling of para-aortic nodes was omitted in 78% of the incompletely staged patients, while 52% of these patients had no pelvic lymph node dissection. Taking blind biopsies from different peritoneal sites was not performed in more than 1/3 of the incompletely staged group. Omission of the staging steps ranged from 3% (infracolic omentectomy) to 55% (biopsy of the right hemi-diaphragm). A significant difference ($p = 0.04$) between the fraction of completely staged patients was found when comparing institutes who entered less than 5 patients (21%) versus those who included more than 20 patients (37%) in the trial.

Conclusions: Even in a randomised trial in which comprehensive surgical staging was strongly advised in the study protocol the majority of patients (66%) were incompletely staged. Factors relating to a lack of surgical skills attributed most to the number of incompletely staged patients, but insufficient knowledge of the tumour behaviour and routes of spread of ovarian cancer also contributed substantially to this problem. Multicentre trials recruiting patients from many institutes with small volume contribution to the study, run the risk of inadequate adherence to the study protocol.

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1. Introduction

Ovarian cancer carries a dismal prognosis[6] and almost the only chance of long-term survival is related to early detection of the disease and a flawless and adequate management of the early stages of this 'silent killer'[7]. An important initial step of such adequate management is a thorough, comprehensive surgical staging procedure.[1,4,5,8] Only the most accurate determination of the extent of the disease will enable the definition of subsets of patients requiring adjuvant therapy and those in whom adjuvant treatment can be considered overtreatment. Consequently, lack of proper staging was found to be an independent prognostic factor in several series.[4,5] In the ACTION Trial the optimally staged patients did not benefit from adjuvant chemotherapy.[5]

Incomplete surgical staging at initial surgery has been reported between 32% and 72% of cases in different studies.[2,9,10] Knowledge of the reasons for the wide spread inadequacy of staging early ovarian cancer is lacking. Only a few studies have addressed this issue[3,9,11] and that is unfortunate, because a change in this aspect of oncology care can only be hoped for if this deficiency can be sufficiently explained.

The EORTC ACTION Trial was one of the largest randomised clinical trials in early ovarian cancer undertaken so far.[5] In this study patients were randomised between observation following surgical treatment and adjuvant platin-based chemotherapy. Detailed information about the staging procedure was available for every patient. These data and other characteristics that might relate to the completeness of surgical staging were analysed.

The aim of the study was to shed more light to the understanding of the reasons for failure of adequate staging surgery in early ovarian cancer.

2. Patients and methods

Between November 1990 and March 2000 448 patients were enrolled in the EORTC ACTION Trial, a randomised clinical trial to study the significance of platinum-based adjuvant chemotherapy in early ovarian cancer. Detailed information of all patients on the staging performance was available and these data were analysed in the present study. Patients were divided in a completely staged group and in an incompletely staged group. If all the staging steps mentioned in Table 1 were completed, staging was considered complete. All other cases were labelled incomplete.

The number of patients entered by the 40 institutes of the 10 participating countries was related to the two staging categories. For the comparison of fractions (complete or incomplete staging) the χ^2 test was used and p-values < 0.05 were considered statistically significant.

3. Results

Clinical and tumour characteristics of the completely and incompletely staged patients are given in Table 2. No differences in mean age, histologic cell type or grade of differentiation of the tumours were seen. In the incompletely staged group the omitted staging steps were divided into two categories: one group of procedures carrying an appreciable risk of surgical morbidity[11] and for which additional surgical skills have to be present and another group of procedures not requiring specific surgical abilities and in which virtually no surgical morbidity was involved. These two groups are shown in Table 3. The surgical morbidity group contributed most to the amount of neglected staging steps. In 78% of incompletely staged patients para-aortic lymph node sampling was not performed followed by 55% omitted biopsies of the right hemi-diaphragm and 52% pelvic lymph node sampling. However, the low morbidity group did also contribute to the total of complete surgical procedures: blind biopsies of paracolic gutters of 39% and blind biopsies of pelvic side wall also of 39%. Even a totally harmless procedure as taking peritoneal washings for cytology was omitted in 33 of 295 incompletely staged patients (11%); Table 3.

The staging categories of the different institutions divided by the number of patients randomised in the trial are listed in Table 4. In total 40 European institutions from 10 countries enrolled in the ACTION Trial. From these 40 centers, 19 centers entered less than five patients, 7 centres between 6 and 10 patients, also 7 centres between 11 and 20 patients and the other 7 centres more than 20 patients. A significant difference was found between the number of patients who were completely staged in the centers which entered a small number of patients (1–5 patients) compared to the centers which entered a large number of patients (>20: 20.5% and 36.5%, respectively, $p = 0.04$). Also a significant difference was shown in the percentage of completely staged patients dividing the centres s into two groups (1–10 patients: 23.2% and >10 patients: 36.7%, $p = 0.01$). Tables 5 and 6 show the number of patients in whom blind biopsies were taken and para-aortic and pelvic lymph node sampling was performed by the four European countries who entered most of the patients in the trial. Pelvic lymph node sampling was carried out in 78% of the patients in Spain while these percentages were 66%, 44% and only 8% for Italy, the Netherlands and Portugal, respectively. On the other hand para-aortic lymph node sampling was performed in 55% of the patients in Italy and the Netherlands while 42% of the patients in Spain and 7% in Portugal had a para-aortic lymph node sampling. Biopsy of the right diaphragm was mostly taken in the Netherlands (74%) compared to 69% in Spain, 58% in Italy and 54% in Portugal. Most of the biopsies from the paracolic gutters and peritoneal side wall were taken in Portugal in 100% and 92% of the patients, respectively.

4. Discussion

In the daily life practice the performance of a complete, comprehensive staging procedure in early ovarian cancer seems to be difficult to accomplish in all patients. In the EORTC ACTION Trial all the necessary staging steps to achieve a complete staging procedure were specifically mentioned in the study protocol and it was strongly advised to execute them. Nevertheless, in 295 of the 448 patients (66%) one or more

Table 1 – Staging steps necessary to arrive at a complete surgical staging procedure for early ovarian cancer following bilateral salpingo-oophorectomy and total abdominal hysterectomy.[a]

Staging guidelines
Inspection and palpation of all peritoneal surfaces
Biopsies of any suspect lesions for metastases
Biopsies or removal of any adhesions surrounding the (area of the) primary tumour
Peritoneal washing
Infracolic omentectomy
(Blind) biopsies of right hemi-diaphragm, of right and left paracolic gutter, of pelvic sidewalls, of ovarian fossa, of bladder peritoneum, and of cul-de-sac
Iliac and periaortic lymph node dissection

[a] Patients with stage Ia disease who wished to preserve fertility were permitted to have only an unilateral salpingo-oophorectomy.

Table 2 – Clinical and tumour characteristics of completely and incompletely staged patients. In two patients the staging status was unknown.

	Completely staged N = 151	Incompletely staged N = 295	*p*-Value
Age	56	54	0.73
FIGO stage			
Ia	46 (30.5%)	109 (36.9%)	
Ib	13 (8.6%)	24 (8.1%)	
Ic ov surf	24 (15.9%)	26 (8.8%)	0.29
Ic caps rupt	38 (25.2%)	78 (26.4%)	
Ic			
Asc/wash	18 (11.9%)	39 (13.2%)	
IIa	12 (7.9%)	19 (6.4%)	
Histologic type			
Serous	45 (30.0%)	111 (38.3%)	
Mucinous	29 (19.3%)	48 (16.6%)	
Endometrioid	44 (29.3%)	76 (26.2%)	
Clear cell	25 (16.7%)	38 (13.1%)	0.65
Undifferentiated	3 (2.0%)	5 (1.7%)	
Other	2 (1.3%)	6 (2.1%)	
Unknown	2 (1.3%)	6 (2.1%)	
Differentiation grade			
Well	15 (9.9%)	39 (13.2%)	
Moderately	87 (57.6%)	142 (48.1%)	0.30
Poorly	47 (31.1%)	109 (36.9%)	
Unknown	2 (1.3%)	5 (1.7%)	
Trial arm			
Observation	75 (49.7%)	147 (49.8%)	0.97
Platin-based chemotherapy	76 (50.3%)	148 (50.2%)	

staging acts had been omitted. This is a sobering finding because one of the consequences of clinical trials is that they keep the participating clinician focused on the state-of-the-art approach of a particular patient group in the study protocol. Admittedly, the criteria in the ACTION Trial to qualify for a complete staging procedure were very strictly applied, but a minority of 1/3 of completely staged patients remains a disappointingly low figure, and this sheds great doubts on the daily life practice outside a trial situation. Furthermore we know from the results of the ACTION Trial published earlier[5] that only the suboptimally staged patients benefit from adjuvant platin-based chemotherapy and the optimally staged patients do not need further treatment. To do something about this deficiency in patient care requires insight into the reasons why comprehensive staging for all patients with early ovarian cancer is so hard to achieve.

One of the reasons may be that the first diagnosis or suspicion of early ovarian cancer is frequently made during a surgical procedure for an acute abdomen or for symptoms of an ovarian cyst and therefore is unexpected. These procedures are normally undertaken by general gynaecologists without surgical skills to perform a proper staging and without the necessary knowledge of tumour behaviour and sites at risk for tumour spread.

We have tried to differentiate between a lack of surgical skill (more difficult procedures with morbidity involved) and a lack of sufficient knowledge of risk sites for ovarian cancer metastases (easy procedures without appreciable morbidity

Table 3 – Omitted staging steps in early ovarian cancer patients.

Procedure not performed	Number of 295 incompletely staged patients	%
Procedure difficult or associated with increased morbidity		
Biopsy of right diaphragm	161	55
Sampling para-aortic Lymph nodes	230	78
Sampling of pelvic Lymph nodes	153	52
Infracolic omentectomy	10	3
Easy procedure; no morbidity involved		
Biopsies of paracolic gutters	114	39
Biopsies of side wall	116	39
Peritoneal washing	33	11

Table 4 – Staging category by number of patients randomised per centre.

Number of patients randomised per centre	Staging category		
	Number of institutes (N = 40)	Complete (%)	Incomplete (%)
1–5	19	20.5	79.5
6–10	7	25.9	74.1
11–20	7	36.8	63.2
>20	7	36.5	63.5

risk). In the former category retroperitoneal lymph node retrieval was neglected in 78% and 52% of incompletely staged patients. These findings concur with those of a similar study in Dutch patients (70%),[11] and those of an earlier study from the United States.[9]

In the group of easy procedure the sites most commonly omitted in the present study were the paracolic gutters (39%), pelvic side wall peritoneum (39%) and even peritoneal washings (11%). In the Dutch study mentioned before, the figures were similar for the peritoneal washings (10%) but very different for the paracolic gutters (85–90%) and the pelvic side wall (73%).[11]

As it seems that lack of surgical expertise as well as deficient knowledge of ovarian cancer spread are responsible for the staging problem at hand, a solution for these short comings has to be solved rather in the organisation of health care programs and subspecialisation of gynaecologic oncologists than in the sheer education of general gynaecologists. Only a more efficient referral policy could serve to have the surgical staging procedures concentrated by gynaecologic oncologists with not only the skills and knowledge to do it, but also the maintenance of experience to deal with a relatively infrequent condition. In this context a policy of only removing a suspicious ovarian cyst or mass and waiting for the definite pathology might help to organise the place and the surgeon for a proper staging procedure later, more effectively.[12–14] In the preoperative evaluation of an adnexal mass, the widely used Risk of Malignancy Index (RMI) which is based on menopausal status, ultrasound morphology of adnexal masses and absolute level of serum CA-125 may help in differentiating between a benign or malignant mass with a sensitivity from 71% to 88% and a specificity ranging between 74% and 89% in different studies.[15–17] The results of a multi centre study, the International Ovarian Tumor Analysis (IOTA), show that pattern recognition by ultrasound correctly classified 93% of the tumours as benign or malignant while serum CA-125 correctly classified at best 83% of the masses.[18]

The ACTION Trial was a multi centre randomised trial and performed by clinical research groups consisting of different types of hospitals. We found in this study a clear correlation in the number of patients enrolled by the different institutes and the surgical staging category. Institutes who entered less than 5 patients performed complete staging in 20.5% of the patients, while this percentage increased to almost 37 if more than 10 patients per institute were enrolled in the trial. The volume issue is important in oncology. In a population-based study of 2450 ovarian cancer patients done by Ioka and colleagues, patients receiving care in very low volume hospitals were seen to have a 60% high risk of death than patients receiving care in high volume hospitals ($p < 0.01$).[19] Vernooij and colleagues[20] found that the level of specialisation and the volume of the hospital were strongly related to the

Table 6 – Lymph node sampling by country of randomisation.

Country	Lymph node sampling performed		
	Number of patients randomised	Pelvic	Para-aortic
Italy	311	206 (66%)	130 (41.9%)
Spain	51	40 (78.4%)	28 (54.9%)
The Netherlands	43	19 (44.2%)	24 (55.8%)
Portugal	13	1 (7.7%)	1 (7.7%)

Table 5 – Blind biopsies by country of randomisation.

Country	Blind biopsies performed			
	Number of patients randomised	Side wall	Paracolic gutters	Right hemi-diaphragm
Italy	311	241 (77.5%)	224 (72%)	179 (57.7%)
Spain	51	40 (78.4%)	27 (52.9%)	35 (68.6%)
The Netherlands	43	28 (65.1%)	36 (83.7%)	32 (74.4%)
Portugal	13	12 (92.3%)	13 (100%)	7 (53.8%)

proportion of adequately staged patients and the overall survival was best in patients treated in specialised hospitals and by high volume gynaecologists.

The conclusion of all this is, that if we allow too many institutes that enrol a low volume of patients in multi centre clinical studies, we run an increased risk of inadequate adherence to the study protocol. We may have to monitor in future trials more carefully the violation of the study protocol with quality control during the study. In the case of early ovarian cancer this means suboptimal performance to follow the required steps of surgical staging.

Conflict of interest statement

None declared.

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