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Does paraaortic lymphadenectomy have a benefit in the treatment of ovarian cancer that is apparently confined to the ovaries?

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Abstract

We conducted a retrospective review of all epithelial ovarian carcinoma patients with disease that is apparently confined to the ovaries who were treated in the Obstetric and Gynecologic Hospital of the University of Tours. In our hospital, no lymphadenectomies for such epithelial ovarian carcinoma patients are carried out. We studied the survival of these patients that were operated upon from 1 December 1975 until 1 August 1997. 43 epithelial ovarian carcinoma patients were studied; 22 were stage Ia, 1 was stage Ib and 20 were stage Ic. The average age was 58 years (range 27–86 years). 5% (2/43) developed recurrent disease and the rates of disease-free and overall survival after 5 years were 83% and 90.3% respectively. These results are very close to those described in literature for patients who underwent paraaortic and pelvic lymphadenectomy. As no series to date has demonstrated the benefit of paraaortic lymphadenectomy on survival and we know that paraaortic lymphadenectomy increases morbidity, we think it reasonable to propose surgery without lymphadenectomy for the treatment of early ovarian epithelial cancer patients whose disease is apparently confined to the ovaries.

Keywords: Epithelial ovarian cancer stage I; Survival; Lymphadenectomy

1. Introduction

Despite the small size and the intra-abdominal position of the ovaries, the diagnosis of stage I ovarian cancer is more and more frequent following the introduction of laparoscopy and intravaginal ultrasonography.

Contrary to other gynaecological cancers, the positive lymph nodes of ovarian cancers are located around the paraaortic and pelvic regions. Moreover, in stage I cancers, it is possible to find pelvic or paraaortic lymph node involvement. These tumours are reclassified, according to the International Federation of Gynecologists and Oncologists (FIGO), as stage IIIc, thus disrupting completely the prognosis and therapy.

There are few data and no consensus on the role of lymphadenectomy in stage I ovarian cancer. It is unclear whether lymphadenectomy is a staging procedure, a therapy, or whether it should be done at all. Many authors [1–9] and the FIGO have recommended comprehensive surgical staging in early ovarian cancer. However, not all patients with early ovarian cancer are suitable for lymphadenectomy. Some authors have demonstrated that surgical treatment alone was sufficient and effective for stages Ia and Ib of grades 1 or 2, and that adjuvant chemotherapy did not modify overall and disease-free survival (DFS) of those patients [5,10,11].

In this paper we studied, retrospectively, 43 patients treated for epithelial ovarian cancer that was apparently confined to the ovaries and regarded as stage I. They were treated at the Obstetric Gynecologic Hospital of the University of Tours, over a 22-year time-period. We believe that paraaortic and pelvic lymphadenectomy during the surgical treatment for early stage cancers increases the morbidity of the operation and decreases the comfort of the patients who have been operated upon, without bringing any proven benefits in terms of improved survival. We therefore do not perform such

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lymph adenectomies. The aims of this study were to assess the results of our patient group in terms of survival and to try to determine from a study of the literature, the likelihood of pelvic and paraaortic lymph node involvement according to several biological and clinical factors (such as stage, type and histological grade). These elements should help to define the importance of pelvic and paraaortic lymphadenectomy in the treatment of early ovarian epithelial cancers.

2. Patients and methods

247 patients with ovarian epithelial carcinoma were treated at the Obstetric Gynecologic Hospital of the University of Tours between 1 December 1975 and 1 August 1997. All of these patients were classified according to FIGO. 43 patients had stage I ovarian epithelial carcinoma (17%). Tumours of low malignant potential, ovarian metastases and tumours other than epithelial tumours were not studied.

Chest radiography, a liver and pelvic ultrasonography, a standard biological and liver check-up, as well as serum CA 125 and ACE measurements were carried out before or after the operation, depending on whether or not the tumour was considered suspect before the operation. To assess the involvement of the paraaortic and pelvic lymph nodes, a lymphography or pelvic and abdominal computed tomography (CT) scan were carried out. A vertical incision was made that was of sufficient length to allow the evaluation of the abdominal contents and the sites of high risk for surface metastases. First of all, a complete abdominal exploration was carried out (liver, lymph nodes, ...) along with an assessment of the peritoneal cytology and multiple peritoneum biopsies were taken. This was followed by a total abdominal hysterectomy, a bilateral salpingo-oophorectomy, a partial infracolic omentectomy and appendicectomy when there were mucinous tumours. Complete paraaortic and pelvic lymphadenectomy was not part of the protocol. The retroperitoneal space was explored by palpation of the pelvic and paraaortic regions and sampling was only carried out when the nodes were suspicious.

The histological type and grade was assessed. The latter was rated from 1 to 3 according to the following criteria: grade 1, well differentiated tumours; grade 2, moderately differentiated tumours; grade 3, poorly differentiated tumours.

For stages associated with a risk of recurrence (stage Ic and stages Ia–Ib with grades 2–3), adjuvant chemotherapy alone or an abdominal and pelvic irradiation alone was carried out (22.5 Grays in the abdomen increasing to 45 Grays in the pelvis). For stages Ia or Ib with grade 1, no adjuvant therapy was given.

3. Results

At the time of the operation, the average age of the patients was 58 years (range 27–86 years). 8 (19%) patients were still menstruating.

The characteristics of each patient are shown in Table 1. Of the 43 patients, 22 (51%) were stage Ia, 1 (2%) was stage Ib and 20 (47%) were stage Ic. 21 (49%) were grade 1, 12 (28%) were grade 2 and 8 (19%) were grade 3. No patient underwent lymph node sampling because the palpation of the pelvic and paraaortic regions was normal for each patient.

49% (21/43) of the cancers had rather a high risk of lymph node metastases (serous or with clear cells). At least 24 (56%) patients had a negative peritoneal cytology. After surgery, there was no residual tumour. Some patients (12%) did not have an omentectomy, for they had a very slight risk of recurrence, and because the diagnosis of ovarian epithelial carcinoma had been made after surgery.

Adjuvant treatment was given to 25 patients (58%): 10 had chemotherapy and 15 had radiotherapy (Table 1). 6 patients refused an adjuvant therapy: 4 with stage Ia, grade 2: 1 serous carcinoma, 1 endometrioid carcinomas, 2 with clear cell carcinomas; 2 with clear cell carcinomas who were positive for peritoneal cytology: 1 stage Ia, grade 3 and 1 stage Ic, grade 2. One patient with stage Ia, grade 1 and a serous ovarian carcinoma was given chemotherapy. One other with stage Ia, grade 2, an endometriod ovarian carcinoma asso-

Table 1
Patient characteristics and adjuvant therapy

Tumour description	*n* (%)	Chemotherapy	Radiotherapy
Tumour stage			
Ia	22 (51)	2	2
Ib	1 (2)	0	1
Ic	20 (47)	8	12
Tumour grade			
1	21 (49)	2	7
2	12 (28)	4	2
3	8 (19)	1	6
Unknown	2 (5)	3	0
Tumour histology			
Endometrioid	14 (33)	3	6
Serous	13 (30)	5	3
Mucinous	8 (19)	2	2
Clear cell	8 (19)	0	4
Peritoneal cytology			
Positive	13 (30)	2	8
Negative	24 (56)	3	6
Unknown	6 (14)	5	1
Omentectomy			
First time	33 (77)	8	11
Second time	5 (12)	1	1
Did not receive	5 (12)	1	3

Table 2
Overall survival

Survival (years)	3	5	10	15	20
Cancer-related deaths	90.3	90.3	86.8	80.1	80.1
All deaths	88.1	88.1	80.3	74.1	59.3
Disease-free survival (without recurrence)	85.7	83.0	75.6	69.8	55.8

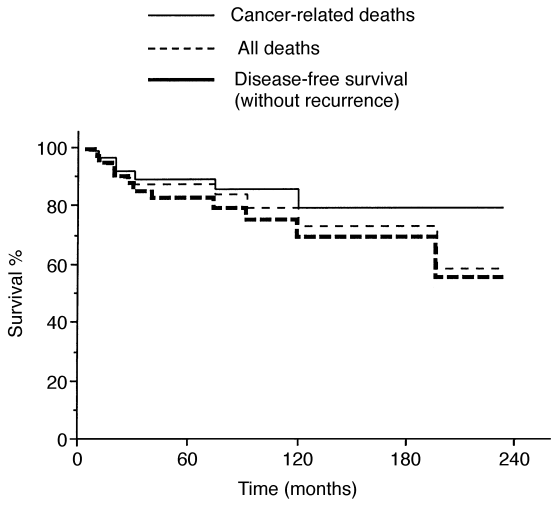

Fig. 1. Overall survival. Three curves are represented: one represents the cancer-related deaths, another curve represents all deaths during the same period of time and the other curve shows the disease-free survival (without recurrence). The respective 5-year survival rates were 90.3%, 88.1%, and 83%.

ciated to a cancer of the corpus of the uterus was given radiotherapy.

For those patients alive at censor date, median follow-up was 98 months (range 16–246). Among the 43 patients, 31 (72%) were in good health, 2 (5%) developed recurrent disease (liver metastases or carcinosis) while undergoing chemotherapy or in remission, 8 patients (19%) died of their disease, 2 patients (5%) died of heart attacks and 2 (5%) patients (stages Ia and Ib) were lost to follow-up after they left the hospital. The patient with stage Ia, grade 3 who refused chemotherapy is still alive at censor date. The patient with a stage Ic, grade 2 carcinoma who refused adjuvant therapy died.

The overall and disease-free survival was studied using the Kaplan–Meier method (Table 2) and is illustrated in Fig. 1. 5-year survival rates of 90.3%, 88.1%, and 83% were obtained for cancer-related deaths, all deaths and DFS (without recurrence) respectively. 6 patients died from their ovarian epithelial cancer an average of 28 months after surgery (range 9–84 months) (Table 3). They all had a stage Ic cancer with the exception of one patient. This patient had a serous histological type and the cancer was stage Ia, grade 1. They were not given any adjuvant therapy and died 7 years (84 months) after surgery with an abdominal carcinosis.

The 5 other patients with grade Ic carcinomas all received adjuvant therapy with the exception of one patient who died 11 months later with liver metastases. 3 of them had an abdominal carcinosis. 2 patients had recurrences. However, no patients had either retroperitoneal or lymph node recurrences in the pelvic and abdominal CT scans. Both recurring patients had grade 3 carcinomas and received adjuvant therapy. One of them with a stage Ib serous type carcinoma is doing well despite an abdominal carcinosis and liver metastases, while the other one with a stage Ic carcinoma of the endometrioid type is undergoing chemotherapy for liver metastases.

4. Discussion

So is it necessary to do a lymphadenectomy? If not, could we determine the risk of lymph node metastases by the histological type and/or grade? Or does paraaortic and pelvic lymphadenectomy have a real benefit in terms of the quality of life and the survival of the patient?

Table 3
Causes of death or recurrences

No.	Age (years)	Stage	Grade	Peritoneal cytology	Histology	Surgery	Chemotherapy	Radiotherapy (Gy)	Recurrence or death (months)	Cause of recurrence or death
1	86	Ia	1	-	S	HT + O	No	No	D (84)	P
2	48	Ic	?	?	S	HT	Yes	No	D (9)	P
3	33	Ic	1	+	CC	HT + O	No	70	D (15)	P and Br
4	53	Ic	2	+	CC	HT + O	No	80	D (17)	P and Li
5	62	Ic	2	+	CC	HT + O	No	No	D (11)	Li
6	50	Ic	?	-	CC	HT + O	No	77	D (29)	Bn, Li, Lu
7	68	Ib	3	+	S	HT	No	67	R	P, Li
8	59	Ic	3	+	E	HT + O	No	45	R	Li

Bn, bone metastases; Br, brain metastases; Bw, bowel metastases; CC, clear cell; D, death; E, endometrioid; HT, hysterectomy; Li, liver metastases; Lu, lung mestatases; O, omentectomy; P, peritoneal; R, recurrence; S, serous.

Table 4
Clinical stage and lymph node involvement

Authors [Ref.]	*n*	Stage I (%)	Stage II (%)	Stage III (%)	Stage IV (%)
Onda [12]	110	7/33 (21)	6/26 (23)	29/43 (67)	6/8 (75)
Wu [2]	77	1/7 (14)	3/8 (38)	38/59 (64)	3/3 (100)
Di Re [3]	253	16/128 (13)	6/26 (23)	46/82 (56)	11/17 (65)
Benedetti-Panici [14]	81	5/35 (14)	0/2 (0)	30/44 (68)	-
Burghardt [13]	180	9/37 (24)	7/14 (50)	84/114 (74)	11/15 (73)
Total	701	38/240 (16)	22/76 (29)	227/342 (66)	31/43 (72)

Onda and colleagues [12] and other authors such as Wu and colleagues [2] and Burghardt and colleagues [13] had shown an increase of lymph node metastases with increasingly advanced clinical stage. In the study by Burghardt and colleagues [13], this lymph node involvement rate was doubled for each increase in stage between stages Ia and III. Benedetti-Panici and colleagues [14] observed lymphatic spread for 14% of stage I patients and this seemed to be limited to only a few lymph nodes and to one pelvic or aortic lymphatic group. Thus, in the literature, the average rate of lymph node involvement in reported stage I is 16% (13–24%, Table 4).

Di Re and colleagues [3] observed that the incidence of lymph node metastases increased with the spread of the ovarian carcinoma. This was particularly true for serous adenocarcinomas and was characterised by a high incidence of node metastases even in stage I patients (27%). The incidence was 3 or 4% for mucinous and endometrioid adenocarcinomas, respectively. In contrast, Benedetti-Panici and colleagues [14] showed there is a relationship between tumour dedifferentiation and the frequency of lymphatic metastases, particularly in stage I, but no conclusions could be drawn about the histotype because of the limited number of cases. Knapp and colleagues [15] have reported in intraabdominal early stage ovarian cancers that lymph node metastases occur predominately in patients with undifferentiated and serous stage Ic cystadenocarcinomas. Thus, serous and clear cell ovarian carcinomas are characterised by a high incidence of nodes metastases in stage I cancers.

Wu and colleagues [2] and Benedetti-Panici and colleagues [14] reported that the degree of differentiation seemed to have no apparent effect on the incidence of lymph node metastases (Table 4). However others [1,3] found that the incidence of metastases increased with an increase in the histological grade. The incidence doubled from grade 1 to grade 3 for stage I patients [16,17].

What is the incidence of paraaortic lymphatic spread without pelvic lymphatic spread? In the literature, different studies on early ovarian cancers (stage I) have shown 0–5.6% paraaortic lymph node involvement with a mean value of 3.8% and a mean of 10% of paraaortic lymph node involvement with or without pelvic lymph node involvement [6,13,15,18]. However, all the studies included very few patients (20–46) with the exception of studies by Lang [18] and Di Re and colleauges [3]. To conclude, for every 100 patients with an early ovarian cancer, approximately 16 patients will have lymph node involvement with 8 having paraaortic lymph node metastases. Furthermore, no more than 3 patients will have isolated paraaortic lymph node metastases (without pelvic lymph node metastases). Moreover, the rate of lymph node involvement increases with the grade. Thus, if we treat with adjuvant therapy every stage Ic and stage Ia–Ib with grades 2–3, only 1 patient with paraaortic lymph node metastases will not receive adjuvant therapy.

Different studies without systematic lymphadenectomy (only sampling where there were suspicious nodes) were reported in literature. Ahmed and colleagues [19] in an important series with no adjuvant therapy after surgery, identified after a multivariate Cox's regression analysis, grade, presence of ascites and surface tumour as independent poor prognostic factors for survival and they found a rate of overall survival for

Table 5
Survival in studies without systematic lymphadenectomy

Authors [Ref.]	*n*	Stage	Survival at 5 years
Young [5]	81	Ia + Ib = 76 + 5	94% O
Dembo [20]	509	I	79% DF
Ahmed [19]	194	Ia/Ib/Ic	94%/92%/84% O
Villa [22]	150	Ia-Ib/Ic	91%/80% O
This study	43	I	90.3% O

O, overall survival; DF, disease-free.

stage Ia patients of 94% (Table 5). For Dembo and colleagues [20] in two retrospective studies of early ovarian cancer in stage I, differentiation was the most important predictor of outcome. The rate of DFS after 5 years was 98% in stage I, grade 1 (Table 5) and 79% for all grades (1–3) in stage I. The extremely low risk of relapse is noteworthy because the majority of these patients received either no post-operative treatment or pelvic irradiation, which has been shown to be ineffective in stage I.

For Finn and colleagues [21] in a retrospective study of stage I ovarian cancer with biopsy of the paraaortic lymph node, grade was also the most important predictor of outcome as demonstrated previously by Dembo and colleagues [20]. The biological behaviour of this disease when confined to the ovary appears to be totally different from the more aggressive advanced disease. Adjuvant chemotherapy and adequate surgical staging, as defined by FIGO, confer no benefit in stage I ovarian cancer and may, in fact, be detrimental to outcome. In contrast, Villa and colleagues [22] showed tumour grading was the main factor in the identification of patients with early ovarian cancer who could benefit from adjuvant chemotherapy (Table 5). In this study, we obtained an overall survival rate of 90.3% at 5 years without lymphadenectomy, which seems to be close to the results from the literature.

Lang and associates [18] and Faught and colleagues [10] in two prospective studies of patients undergoing paraaortic lymphadenectomy for stage I cancer found a survival rate of approximately 96%, which is very close to that found by other authors in studies where patients did not undergo lymphadenectomy. Petru and associates [9] in a retrospective study of 100 patients with stage I ovarian cancer found that 7/40 (18%) of patients who had a lymphadenectomy had recurrent disease; all these recurrences were located intraperitoneally or at distant sites. In contrast, in the 8/60 (13%) patients who had a recurrence, but had not undergone a lymphadenectomy, 7 recurrences had a retroperitoneal component. The distribution of risk factors was different in the two groups with more stage Ic patients in the group that had lymphadenectomy. However, the failure rate was no better for the patients who recurred who had lymphadenectomy compared with those who recurred without undergoing a lymphadenectomy.

For Soper and associates [8], the determination of early stage disease and host tumour biology may be the most important factors in determining the survival of women with early ovarian cancer defined by comprehensive surgical staging. Onda and colleagues [23] observed that patients with epithelial ovarian carcinoma restaged from stage I/II to stage IIIC after systematic lymphadenectomy had a similar survival to stage I/II patients and superior survival to other stage III patients. However, these studies were retrospective and the authors could not prove that this procedure had a therapeutic benefit. No series could demonstrate the benefit of lymphadenectomy for the survival of stage I patients, as no randomised prospective trial (with or without lymphadenectomy) has ever been carried out. On the contrary, we know that lymphadenectomy increases morbidity.

5. Conclusion

The importance of an optimal surgical exploration in order not to underestimate an apparently early stage, seems to us to be fundamental in the treatment of ovarian epithelial cancers.

The morbidity of paraaortic lymphadenectomy is not always reported by the teams who carry it out and its completion is not easy to achieve for any surgeon whatever the technique used and thus should be avoided where it is not necessary.

Our experience with 43 patients provides data that recurrences in the peritoneum may be detrimental to survival. However, it is uncertain whether paraaortic lymphadenectomy would have prevented such reoccurrences. The survival rates obtained in this study were very close to those found in the literature.

The study of the literature does not provide any series that shows clearly the advantage of paraaortic lymphadenectomy. Since early stage ovarian epithelial cancers are scarce, prospective studies are not possible. These alone could determine the importance or not of paraaortic lymphadenectomy on survival.

As all stage Ic and all stage Ia–Ib with histological grades >1 will receive adjuvant chemotherapy or radiotherapy and given that lymphadenectomy increases morbidity, we think it reasonable to propose surgery without lymphadenectomy for the treatment of early ovarian epithelial cancer. However, to provide solid evidence that this procedure (with or without lymphadenectomy) has a therapeutic benefit, randomised controlled studies are needed.

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