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Lymphadenectomy in surgical stage I epithelial ovarian cancer

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Key words
Ovarian epithelial cancer, lymphadenectomy, surgical staging, lymph node dissection, lymph node metastases

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Conflicts of interest
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Abstract

Objective. To identify the extent of lymphadenectomy performed in women presenting with epithelial ovarian cancer macroscopically confined to the ovary. Furthermore, the effect of lymphadenectomy on overall survival is evaluated. *Design.* A prospective nationwide case-only study. *Setting.* Denmark 2005–2011. *Sample.* All women registered in the nationwide Danish Gynecologic Cancer Database from 1 January 2005 to 1 May 2011, presenting with a tumor macroscopically confined to the ovary without visible evidence of abdominal spread at the time of the initial exploration (surgical stage I). *Method.* Descriptive and survival analyses of data from Danish Gynecologic Cancer Database. *Main outcome measures.* The annual proportion of women with surgical stage I disease who received lymphadenectomy and the survival in the two groups. *Results.* Of 2361 women with epithelial ovarian cancer, 627 were identified with surgical stage I. Lymphadenectomy was performed in 216 women (34%) of whom 13 (6%) had lymph node metastases. At 5-year follow up 85% remained alive in the lymphadenectomy group compared with 80% in the control group ($p = 0.064$). The lymphadenectomy fraction increased from 24% in 2005 to 55% in 2011. When univariate and multivariate analyses were conducted only an insignificant difference in the survival probability was found between lymphadenectomy and no lymphadenectomy in women presenting with tumor macroscopically confined to the ovary. *Conclusion.* Although increasing, the number of women with surgical stage I disease in Denmark who receive lymphadenectomy remains low, but this did not seem to make a difference to survival.

Abbreviations: DGCD, Danish Gynecological Cancer Database; HR, hazard ratios.

Introduction

Ovarian cancer is the 11th most common cancer among women in Denmark (1). The incidence is 18/100 000 and the overall 5-year survival is 39% (1,2). The cornerstone of the effort to increase survival in ovarian cancer is early

Key Message

The number of unstaged patients with early ovarian cancer is high. As lymphadenectomy may increase morbidity and as the survival benefit is questionable, the procedure will be subject to ongoing research and discussion in the Danish Society of Gynecologic Oncology.

detection and centralization of treatment with correct surgical staging and complete resection of the tumor followed by adjuvant chemotherapy (3–5). The initial staging of ovarian cancer is performed during the primary operation and the final stage is adjusted according to the findings of the pathological examination (5).

Accurate surgical staging is essential for the choice of postoperative treatment and the provision of prognostic information to the patient (3,5). The prognosis is stage-specific with 5-year survival rates in Denmark ranging from 83% for stage I, 62% for stage II, 22% for stage III and only 11% for stage IV (2). Whether adjuvant chemotherapy should be provided is governed by the disease stage and accurate staging can spare women both over- and under-treatment. For stage Ia and Ib with Silverberg histological grade 1 adjuvant chemotherapy is not recommended. For stage Ia and Ib with Silverberg histological grade 2 and 3, stage Ic, stage IIa and all clear cell carcinomas, adjuvant chemotherapy with at least three cycles of carboplatin and paclitaxel is recommended. For stage IIb–IV adjuvant chemotherapy with at least six cycles of carboplatin and paclitaxel is recommended (5).

Lymphadenectomy is part of the surgical staging with the aim of clarifying lymph node status by pelvic resection of the external iliac, internal iliac, obturator and common iliac lymph nodes bilaterally, para-aortic lymph nodes around the aorta and vena cava proximal to the aortic bifurcation. Intraoperatively, stage I appears to be macroscopically confined to the ovaries. However approximately one in five patients are subsequently upstaged to IIIC due to lymph node metastases (6). Although newer imaging techniques such as PET/CT are promising and increasingly used, no noninvasive diagnotic procedure exists to evaluate the lymph node status and as a consequence adjuvant therapy is needed (7). The required extent of lymphadenectomy to sufficiently stage a woman's disease, as well as the effect of lymphadenectomy on overall survival, remain unknown.

Pelvic lymphadenectomy for stage I was introduced in the Danish Gynecological Cancer Group guidelines in 2008. According to the new national recommendation from 2012 it is now mandatory to resect pelvic and para-aortic lymph nodes bilaterally. Before 2012 paraaortic lymph node resection was only mandatory in cases of clinical or radiological suspicion and was only consistently performed by a few gynecological oncology surgeons. Other staging steps including total hysterectomy, bilateral salpingoophorectomy, peritoneal washings or ascites for cytology, peritoneal biopsies, omentectomy and appendectomy in case of mucinous carcinomas were recommended throughout the period (8).

The primary study objective was to evaluate the Danish nationwide progress in implementing lymphadenectomy for women presenting with tumor macroscopically confined to the ovary at the time of laparotomy (surgical stage I). A second objective was to estimate the effect of lymphadenectomy on the survival for women with surgical stage I disease.

Material and Methods

This study is a nationwide quality study and it is governed by the approval of the Danish Gynecological Cancer Database (DGCD) (Danish Data Protection Agency, case number 2007-58-0014).

The DGCD has existed since January 2005 and is a national clinical database for ovarian, uterine and cervical cancer. It contains detailed clinical basic information from the patients' medical records including information on surgical intervention, pathology and oncology. Registration is mandatory and covers around 97% of all women diagnosed with ovarian, uterine and cervical cancer from January 2005 (2).

Through the DGCD, we identified 2361 Danish women diagnosed with stage I–IV epithelial ovarian cancer between 1 January 2005 and 1 May 2011. Inclusion criteria comprised women presenting with tumor macroscopically confined to the ovary without visible evidence of abdominal spread at the time of the initial surgical exploration, i.e. surgical stage I.

In women who underwent incomplete surgical staging procedures in a general hospital and a secondary restaging operation at a gynecological oncology center, the operations were registered as one primary operation and the woman was included in the lymphadenectomy group. In DGCD it is mandatory to register if no lymphadenectomy was performed or if pelvic and/or paraaortic lymphadenectomy was performed.

As part of the pathology registration it is mandatory for the pathologist to register whether lymph nodes were received and if metastases were found. The number of lymph nodes are not registered. The surgical information was compared with the pathology registration. In cases of conflict, the pathologist or gynecologist was contacted. Discrepancies were found and corrected in 25 cases. In 24 of these women the pathologist had incorrectly registered that no lymph nodes had been received while the surgeon had registered lymphadenectomy correctly.

Statistical analysis

The statistical analyses were conducted using SPSS 18.0 software package (SPSS Inc., Chicago, IL, USA). Survival probability was estimated using the Kaplan–Meier method and tested by a log-rank test (Mantel–Cox). Outcome hazard ratios (HR) were calculated using multivariate Cox analysis. A two-tailed p-Value <0.05 was

considered significant. The follow-up period was from 1 January 2005 to 1 September 2011.

Results

From 1 January 2005 to 1 May 2011, 627 of 2361 women with epithelial ovarian cancer were identified with surgical stage I in the DGCD (Tables 1 and 2). There were 324 women in stage Ia, 48 in stage Ib and 255 in stage Ic. Lymphadenectomy was performed in 216 (34%) women of the 627 with surgical stage I. Lymphadenectomy was performed in 34.3% of surgical stage Ia, 25% of stage Ib and 36.5% stage Ic (Table 3). Of women with surgical stage I disease, 416 did not receive lymphadenectomy, 162 (39%) of these were classified as stage Ic during the surgery. Median follow up for all women was 38 months (quartiles: 21–55; range: 1–76) and for the 76 deceased patients 22 months (quartiles: 9–34; range: 1–60).

In the lymphadenectomy group paraaortic lymphadenectomy was performed in 7% of the women, pelvic lymphadenectomy in 44%, and in 48% both paraaortic and pelvic lymphadenectomy was performed.

In 2005 24% of the women underwent lymphadenectomy and in 2011 this proportion was 55% ($p = 0.007$) (Table 2). At 5-year follow up 85% of women were alive in the lymphadenectomy group and 80% in the control group ($p = 0.064$) (Figure 1). In the multivariate Cox analysis lymphadenectomy (HR = 1.7; 95% CI 0.9–3.0), comorbidity (HR = 1), cyst rupture (HR = 0.9), grade (HR = 1.1) and peritoneal fluid cytology (HR = 1.2) were

Table 1. Final stage, histology and grade for the 627 surgical stage I epithelial ovarian cancer patients.

Baseline	*n*	%
Total patients	627	
Median age (range)	59 (13–90)	
Final stage		
Ia	234	37.3
Ib	18	2.9
Ic	299	47.7
IIa	11	1.8
IIb	6	1
IIc	15	2.4
IIIa	16	2.6
IIIb	7	1.1
IIIc	15	2.4
IV	4	0.6
Unspecified	2	0.3
Total	627	100
Histology		
Serous	192	30.6
Mucinous	131	20.9
Clear cell	71	11.3
Endometrioid	142	22.6
Other	91	14.7
Total	627	100
Grade		
1	239	46.8
2	159	31.1
3	113	22.1
Total	511	100

Table 2. Development in lymphadenectomy at surgical epithelial ovarian cancer stage I in Denmark 2005–2011.

Lymphadenectomy	No	%	Yes	%	Total
2005	80	76.2	25	23.8	105
2006	82	71.9	32	28.1	114
2007	80	67.2	39	32.8	119
2008	62	62	38	38	100
2009	65	61.9	40	38.1	105
2010	37	50.7	36	49.3	73
2011	5	45.5	6	54.5	11
Total	411	65.5	216	34.4	627

Table 3. Lymphadenectomy and metastases in surgical stage Ia, Ib and Ic.

Lymphadenectomy					Metastases	
Stage	No	%	Yes	%	Yes	%
1a	213	65.7	111	34.5	5	4.5
1b	36	75	12	25	2	16.7
1c	162	63.5	93	36.5	6	6.5
Total	411	65.6	216	34.4	13	6.0

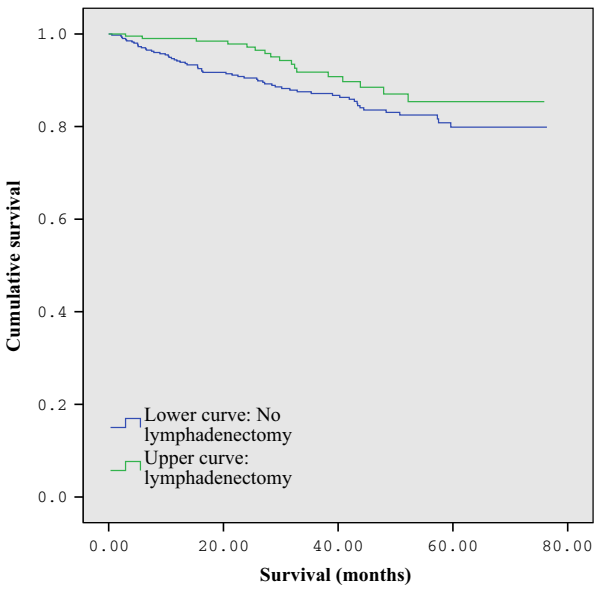

Figure 1. Kaplan–Meier curves for epithelial ovarian cancer patients who received lymphadenectomy ($n = 216$) and patients who did not ($n = 411$). $p = 0.064$ using the log-rank test.

not significant. whereas performance score (HR = 1.9), final stage (HR = 1.2) and histology (HR = 1.1) were significant.

In the lymphadenectomy group 13 women (6%) had lymph node metastases, 202 (94%) had no lymph node involvement and in one woman the pathologist found no lymph nodes in the histological specimen. In women with metastases serous carcinomas were found in nine (75%), endometrioid in two (16.7%) and carcinosarcomas in one (8.3%). In women with no metastases the distribution was 59 (30.3%) serous, 29 (14.9%) mucinous, 35 (17.9%) clear cell, 49 (25.1%) endometrioid, 10 (5%) carcinosarcoma and 13 (6.7%) undifferentiated. Furthermore, there was no significant difference in probability of survival between patients with lymph node metastases and patients without ($p = 0.6$). At the 5-year follow up 76% were alive in the group with lymph node metastases and 86% in the group without lymph node metastases ($p = 0.6$).

Discussion

In Denmark between 2005 and 2011, lymphadenectomy was performed in 34% of all women with tumor macroscopically confined to the ovary (stage I). In 2011 lymphadenectomy was performed in only 55% of women with stage I disease (Table 2) even though it was made mandatory by the DGCD guidelines in 2008. The low proportion of women receiving lymphadenectomy in this study corresponds with the findings of earlier studies (3,9,10). In Denmark, lymphadenectomy is not recommended for stage Ic disease because chemotherapy is advised independent of the lymph node status. However, 416 surgical stage I patients did not receive lymphadenectomy and only 162 (39%) of these were classified as stage Ic during the surgery. An explanation for the discrepancy between guidelines and the clinical reality must be sought elsewhere. A fear of short-term and long-term complications (11–13) without a clearly documented survival benefit (4) may be one of the causes of the low Danish number of pelvic and paraaortic lymphadenectomies, respectively.

In this study, 6% of 216 resected patients had lymph node metastases. In the literature lymph node metastases are reported in 4–27% of resected patients (14). In a review from 2008, 20% of the women had lymph node metastases; 5% in the pelvic nodes, 9% in the aortic nodes and 6% in both pelvic and aortic lymph nodes (15). Only one randomized study of lymphadenectomy for stage I has been published, by Maggioni et al. (6). In this study they found metastasis rates of 18% vs. 4% when comparing lymphadenectomy with lymph node sampling, respectively (6). The total number of lymph nodes removed in our study is unknown. A possible explanation for the relatively low percentage of lymph node metastases in our study could be that fewer lymph nodes were removed than in the study by Maggioni et al. (6). This can partly be explained by the change in Danish Gynecological Cancer Group guidelines, which until 2012 prescribed mandatory pelvic lymphadenectomy, but paraaortic lymphadenectomy only if indicated by clinical or radiological suspicion. One reason for this was that paraaortic lymphadenectomy is generally regarded as a comprehensive and risky procedure requiring more surgical skill. However, this causes concern because several studies have shown that metastases isolated to the paraaortic lymph nodes are a common phenomenon in early-stage ovarian cancer (15,16). According to the new Danish national recommendation from 2012 it is now mandatory to resect pelvic and paraaortic lymph nodes bilaterally and the total number of removed lymph nodes will be recorded in the DGCD in the future.

In this study there was a nonsignificant difference in the probability of survival after lymphadenectomy and no lymphadenectomy in women with a tumor macroscopically confined to the ovary in Denmark in the period 2005–2011 (Figure 1). The presence of metastases had no significant influence on the probability of survival in the present study. However, as only 6% of women with lymphadenectomy had metastases and as the number of events was low, this may represent a power problem. In the randomized study by Maggioni et al. an insignificant increase in overall survival is found when comparing lymphadenectomy with lymph node sampling (6). So far lymphadenectomy has been regarded as an attempt to stage women's disease and the survival benefit is still debatable (17–19).

Lymphadenectomy may be seen as a method of identifying those women with higher stage disease, who would otherwise have been undertreated. A woman with metastases to the retroperitoneal lymph nodes will be upstaged from stage I to stage IIIC in the FIGO staging system of ovarian cancer. This upstaging results in a change in the postoperative treatment from either nothing or three cycles of chemotherapy to at least six cycles, and it results in a decreasing 5-year survival rate from 83% to 23%. Lymphadenectomy also makes it possible to spare some women from chemotherapy as studies on adjuvant chemotherapy in ovarian cancer stage I find no benefit of adjuvant chemotherapy in women with no lymph node metastases (3).

To balance the risk of lower survival for women with stage I disease not receiving systematic lymphadenectomy compared with women receiving systematic lymphadenectomy (3), the Danish guidelines recommend chemotherapy for this group. Unfortunately, the Danish national registration of oncologic treatment is still too incomplete for valid analyses of treatment in this study.

This is the first study on lymphadenectomy including all cases of ovarian cancer from one nation, treated in a normal clinical day-to-day setting and not in a strict protocol. The study indicates that implementation of new surgical procedures poses a challenge. Changes need to be well founded with a high degree of involvement of the executive surgeons to succeed. Lymphadenectomy may increase morbidity, and the survival benefit may be questionable. Therefore, lymphadenectomy will be subject to ongoing research and discussion in the Danish Scientific Society of Gynecologic Oncology.

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