Role of lymphadenectomy in endometrioid endometrial cancer

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Summary

Objective: To assess the risk factors associated with node involvement. *Study design:* In the period 1990-2008 a total of 265 endometrial cancers were treated in the Institut Universitari Dexeus. We analysed the rate of myometrial invasion, tumour grade, histological type and node involvement. *Results:* Overall, 86% of tumours were endometrioid, 5.3% papillary serous, 4.9% mixed and 2.6% endometrial stroma sarcoma. Among those with endometrioid histology, lymphadenectomy was not performed (NL) in 85 cases (37.2%), whereas pelvic lymphadenectomy (PL) or pelvic and aortic lymphadenectomy (PAL) was carried out in 84 (36.84%) and 59 patients (25.87%), respectively. In NL patients the overall disease-free survival (DFS) rate at five years was 92.8%. In the PL group, node involvement was observed in 2.4% of cases and the five-year DFS rate was 92.3%. Among PAL patients, 18.6% showed node involvement (72.7% positive pelvic nodes and 63.6% aortic). Aortic involvement was present in 5.9% of cases when there was no pelvic disease, whereas in the presence of positive pelvic nodes the rate of aortic involvement was 50%. The DFS rate at five years was 93.6%. Referring to the risk factors, when infiltration was > 50% of the myometrium, lymph node involvement occurred in 37% of cases and G3 tumors in 45.5%. *Conclusions:* Node involvement is more commonly observed in cases with > 50% myometrial invasion and G3, accounting for 25% of cases that can be considered as at-risk patients. When node involvement is present it is equally distributed between the pelvic and aortic levels. As node involvement is a predictive factor for distant metastasis, the 25% of patients considered to be at risk should undergo pelvic and aortic lymphadenectomy

Key words: Endometrial cancer; Lymphadenectomy; Management; Paraaortic lymph node; Pelvic lymph node.

Introduction

Endometrial cancer (EC) is the most common gynaecological cancer and its incidence is rising. The standard treatment for EC is hysterectomy with bilateral salpingo-oophorectomy and pelvic and aortic lymphadenectomy, although patients in the early stages can be treated with hysterectomy alone. However, despite adequate surgical intervention the cancer reoccurs in some patients. Some authors propose that lymphadenectomy should only be performed in high-risk patients, as the remainder will not benefit from this intervention and will show higher morbidity rates due to the technique [1-4]. Others suggest starting with pelvic lymphadenectomy and, in the event that this is positive, following up with aortic lymphadenectomy. It has also been argued that only suspicious nodes should be removed, as more than 50% of cases are identifiable macroscopically, with only 5% of hidden metastasis [5, 6]. At all events there is no consensus as to the scope of the lymphadenectomy which should be performed, and prospective findings from the PORTEC and GOG studies [2, 7] appear not to support the need for this intervention. More recently the ASTEC study group [8] have demonstrated that lymphadenectomy has no effect on survival rates.

Given the controversy over the role of lymphadenectomy in endometrial cancer the present study sought to analyse the risk factors for node involvement and determine the usefulness of this procedure in treating patients with endometrial cancer.

Material and Methods

We conducted a retrospective study of 300 patients diagnosed and treated for endometrial cancer during the period 1990-2008. Thirty-five were excluded: 12 patients presented a concomitant ovarian neoplasm and in 23 there was insufficient clinical data. The final sample comprised 265 patients. The mean age of patients was 58.8 years (SD 11.6, range 29-95). Of the total, 86% (228) showed endometrioid histology and 14% (37) non-endometrioid. Surgical staging included lymphadenectomy in 161 (60.7%) patients, being pelvic in 89 cases and both pelvic and aortic in 72 cases. During the first period the indication for aortic lymphadenectomy was positive pelvic nodes. Since 2002 pelvic and aortic lymphadenectomy have been performed in high-risk patients. In this study the surgeon made the final decision whether or not to perform lymphadenectomy. A preoperative biopsy was performed to assess invasion and histological grade.

The surgical procedure began by collecting peritoneal fluid or with a peritoneal wash for cytological analysis. This was followed by extrafacial hysterectomy, with the surgical sample being sent for intraoperative biopsy. Pelvic lymphadenectomy included the dissection of all the nodes of the common, external and internal iliac vessels, as well as all the fatty and lymph tis-

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sue above and to the side of the obturator nerve. Aortic lymphadenectomy included the dissection of all nodes and fatty tissue around the aorta and vena cava, from the bifurcation of the aorta to the level of the left renal vein. The mean number of pelvic nodes obtained per patient was 17 (range 2-33), while the mean number of aortic nodes was 7 (range 1-24).

Patients were classified into two groups according to clinical parameters, tumour grade, myometrial invasion, lymphovascular space involvement and histological type. Low-risk patients were: endometrioid histological type, < 50% myometrial invasion, G1 and G2. High-risk patients were: endometrioid tumours with > 50% myometrial invasion or all G3 or lymphovascular space involvement and all tumours non-endometrioid.

Complementary radiotherapy was administered to high risk patients, always if deemed appropriate by the radiotherapist.

The variables analysed were: myometrial invasion, histological grade, histological type, pelvic and/or aortic node involvement, adjuvant radiotherapy and chemotherapy, reoccurrence and metastasis.

Endometrioid adenocarcinomas were analysed. We also separately analysed those patients in whom a lymphadenectomy had not been performed, those who had undergone a pelvic lymphadenectomy and those who had had both a pelvic and aortic lymphadenectomy.

Statistical analysis

Quantitative variables were compared using either the *t* test or the Mann-Whitney U test depending on the assumptions fulfilled. Qualitative variables were compared using either Pearson's chi-square test or Fisher's exact test. The rate of disease-free survival was estimated via Kaplan-Meier survival models. All tests were bilateral and significance was set at $\alpha = 0.05$.

Results

A total of 265 patients were analysed. Myometrial invasion was absent in 27.7% of cases, whereas in 54.2% there was < 50% invasion, in 16.2% there was > 50% and in only 1.9% of patients was serosal infiltration observed. With respect to tumour grade, 55% were G1, 29.1% were G2 and 11.7% G3. After surgery 214 patients were classified as Stage I, 15 as Stage II, 27 as Stage III and two as Stage IV.

Tumours with endometrioid histology

There were 228 cases with endometrioid histology. Pelvic lymphadenectomy was performed in 84 patients (36.84%) and both pelvic and aortic lymphadenectomy in 59 (25.87%). Among the latter the pelvic lymphadenectomy was complete in 49 cases, and only pelvic sampling in ten patients. The aortic lymphadenectomy was complete in 25 cases, with sampling alone being performed in the remaining 34 patients. The number of pelvic and aortic nodes obtained was, respectively, 17.3 (SD 6.3, range 2-33) and 7 (SD 4.5, range 1-24). Radiotherapy was administered to 23.7% of patients. Eight (3.5%) patients reccurred, but none of the patients with subsequent reccurrence had previously received radiotherapy.

Eleven (4.8%) cases of distant metastasis were detected over a mean follow-up of four years.

Ten patients received chemotherapy, four of which had positive nodes (five were classified as IIIc) and two presented a positive peritoneal wash. Only one of these patients showed distant metastasis, this being a woman with 12 positive nodes (4 pelvic and 8 aortic). The remaining patients with distant metastasis had not received chemotherapy.

Both *pelvic and aortic lymphadenectomy* were performed in 59 patients, their mean age being 56.81 years (SD 10.4, range 29-74). Node involvement was observed in 11 (18.6%) of these patients: this was at the pelvic level in 72.7% of cases, at the aortic level in 63.6% and solely at the aortic level in 27.3%. Furthermore, when pelvic nodes were negative there was only aortic involvement in 5.9% of cases, whereas when the pelvic lymphadenectomy was positive there was also aortic involvement in 50% of patients.

We then analysed node involvement in relation to known risk factors such as myometrial invasion and tumour grade. This showed that in the absence of myometrial invasion, or when this was < 50%, there was node involvement in 2.8% of G1/G2 tumours and 33.3% of G3 tumours. However, with > 50% myometrial invasion or serosal infiltration the rate of node involvement was 45.4% in G2 tumours and 60% in G3 ($p < 0.05$) (Table 1).

Table 1. — *Rate of node involvement according to degree of myometrial invasion and tumour grade in patients with endometrioid tumours who underwent pelvic and aortic lymphadenectomy.*

	G1 (%)	G2 (%)	G3 (%)	Total N+ with respect to degree of myometrial invasion (%)
No myometrial invasion	0	0	0	0
< 50% invasion	2.8	0	33.3	9.7
> 50% invasion	0	40	50	37.7
Serous	0	100	100	100
Total N+ according to tumour grade (%)	4.5	19.2	45.4	$p < 0.05$

The mean age of patients with positive nodes (N+) was 60.6 years (SD 12.4) compared with 55.9 (SD 9.8) for those without node involvement ($p < 0.05$). Radiotherapy was administered to 45.8% of these patients.

After a mean follow-up of 62.9 months two cases of recurrence (3.38%) were detected at six and 122 months. Both these patients were N- (4.1%). Distant metastasis was observed in three cases (5.1%), at 23, 57 and 74 months after diagnosis; these cases corresponded to 18.2% of N+ patients but only 2.1% of N- patients ($p < 0.05$).

Overall disease-free survival (DFS) rate at five years was 93.6%. Broken down by group the DFS rate was 50% for patients with both pelvic and aortic N+, 66.77% in patients with pelvic N+ but aortic N-, and 93.5% for patients with a pelvic N- but aortic N+, as well as in those cases where both were N- (Figure 1, Table 2).

Pelvic lymphadenectomy alone was performed in 84 patients. Node involvement was detected in two of these

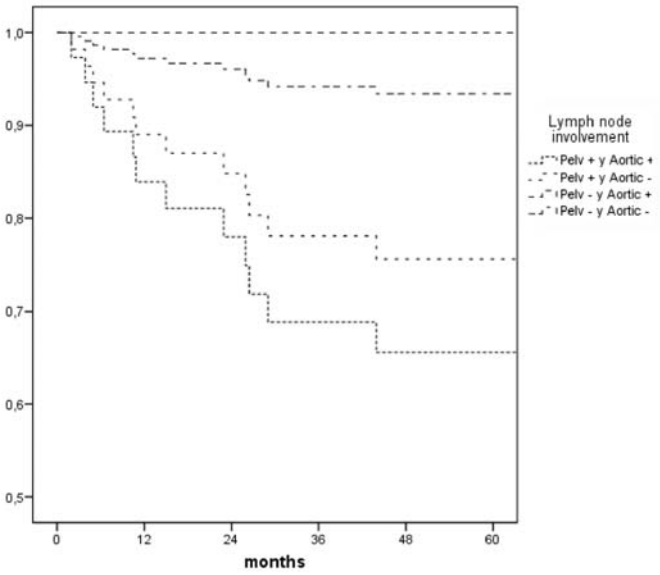

Figure 1. — Survival rate of patients with endometrioid tumours who underwent pelvic and aortic lymphadenectomy according to type of node involvement.

cases (2.4%), the remainder being negative. The mean age of N+ patients was 69 years (SD 4.2) compared with 57 (SD 9.4) for N- patients. Radiotherapy was administered to 20 of these patients (23.8%). There were five cases (6%) of recurrence, none of whom showed node involvement. Distant metastasis appeared in two cases (2.3%), both free of node involvement. The overall five-year DFS rate was 92.3% (Table 2).

No lymphadenectomy was performed in 85 cases (37.2%). Radiotherapy was administered to 8.3% of these patients. One patient (1.2%) with < 50% invasion (G2) had a recurrence. There were six cases of metastasis (7%). Four of these patients were considered to be high risk but the pathology results were deferred, and it was decided not to perform further surgery as three of them were aged over 80. The mean age of patients with metastasis was 74.1 years. The five-year DFS rate was 92.8% (Table 2).

Discussion

In 1988 the International Federation of Gynaecology and Obstetrics (FIGO) [9] stated that correct staging of endometrial cancer required both pelvic and paraaortic lymphadenectomy. Since then it has been proposed that radiotherapy is not necessary when the lymphadenectomy shows there is no node involvement. However, there is little clinical evidence regarding the benefits of lymphadenectomy, a procedure that also increases morbidity [3]. Although large series have reported an improvement in survival rates following lymphadenectomy [10, 11],

Table 2. — *Clinical characteristics of patients according to the type of lymphadenectomy performed*.

	Endometrioid	Pelvic+aortic lymphadenectomy	Pelvic lymphadenectomy	No lymphadenectomy	
N	228	59	84	85	
Age	58.4+11.4	56.8+10.4	57.3+9.5	60.5+13.3	ns
Pelvic nodes	17.4+6.4	18.4+6.4	16.6+6.3		ns
Aortic nodes	7.0+4.6	7.0+4.6			
Stage					
I	190 (84.4%)	38 (65.5%)	74 (88.1%)	78 (94%)	
II	12 (5.3%)	6 (10.3%)	5 (6.0%)	1 (1.2%)	
III	21 (9.3%)	14 (24.1%)	4 (4.8%)	3 (3.6%)	
IV	2 (0.9%)	0 (0.0%)	1 (1.2%)	1 (1.2%)	$p < 0.05$
Radiotherapy	54 (23.7%)	27 (45.8%)	20 (23.8%)	7 (8.2%)	$p < 0.05$
Chemotherapy	10 (4.4%)	8 (13.6%)	1 (1.2%)	1 (1.2%)	$p < 0.05$
Myometrial invasion					
No	63 (28.0%)	10 (16.9%)	12 (14.5%)	41 (49.4%)	
< 50%	126 (56.0%)	31 (52.5%)	60 (72.3%)	35 (42.2%)	
> 50%	32 (14.2%)	16 (27.1%)	10 (12.0%)	6 (7.2%)	
Serous	4 (1.8%)	2 (3.4%)	1 (1.2%)	1 (1.2%)	$p < 0.05$
Grade					
1	133 (59.4%)	22 (37.3%)	53 (63.9%)	58 (70.7%)	
2	70 (31.3%)	26 (44.1%)	23 (27.7%)	21 (25.6%)	
3	21 (9.4%)	11 (18.6%)	7 (8.7%)	3 (3.7%)	$p < 0.05$
Node involvement	13 (5.7%)	11 (18.6%)	2 (2.4%)		$p < 0.05$
Pelvic node involvement	10 (4.4%)	8 (13.6%)	2 (2.4%)		$p < 0.05$
Aortic node involvement	7 (3.1%)	7 (11.9%)			
Reoccurrences	8 (3.5%)	2 (3.4%)	5 (6.0%)	1 (1.2%)	
Metastasis	11 (4.8%)	3 (5.4%)	2 (2.4%)	6 (7.1%)	
Progression	18 (7.9%)	5 (8.5%)	6 (7.1%)	7 (8.2%)	
Disease-free survival rate at 60 months	92.7%	93.6%	92.3%	92.5%	ns

ns: non significant.

with some considering that its scope is a determining factor [12-16], the ASTEC study [8] found no impact on survival. Nevertheless, the authors considered that lymphadenectomy was not contraindicated since it enables a better classification of high-risk patients, thus helping to identify those susceptible to treatment [17]. These results are complemented by the findings of an Italian multi-centre study [18] which randomised 500 patients and also reported no differences in survival rates between the groups. However, both these studies were criticised by Höckel and Dornhöfer [19], who pointed out that the disease was only treated at the pelvic level (pelvic lymphadenectomy and pelvic radiotherapy). Given that in around 30% of cases lymph metastasis occur only at the paraaortic level, and that when the pelvic lymphadenectomy is positive the aortic lymphadenectomy is also positive in 50% of patients, then in approximately 75% of patients with node metastasis these would be outside the pelvic area and, therefore, uncontrolled [19, 20]. Both studies demonstrated effective local control, as there was a 50% reduction in reccurrence rates. Therefore, the results did not translate into improved survival. Adjuvant therapy with paclitaxel-carboplatin may be the best option in these cases. Another criticism of this study was that in the standard surgery group the surgeon could remove the pelvic nodes if it was considered of benefit to the woman. This concession contradicts the stated aim of the study, which was to assess the therapeutic effect of lymphadenectomy. Moreover, the fact that 43% of patients included were low risk dilutes the possible therapeutic effect of lymphadenectomy, and it should also be noted that half the patients had 12 or fewer nodes [20, 21]. Other studies have shown that 12 nodes is the minimum number for correct staging [21, 22], although there is no consensus regarding the most suitable number. Finally, the sample size of this study was also criticised due to the low proportion of N+ patients [20].

In our series none of the patients with a recurrence had received radiotherapy, thus supporting the notion of better local control following this treatment. In recent years, since publication of the PORTEC 2 trial [23] which demonstrated that brachytherapy offered the same degree of local control as external radiotherapy but with less morbidity, the majority of patients have received radiotherapy in the form of brachytherapy. In terms of the type of surgery performed it can be seen that the subgroup of patients with an endometrioid tumour and in whom a lymphadenectomy was not carried out constituted a lower risk subgroup; consequently, radiotherapy was only administered to 8.3% of these patients, although even so the rate of recurrence was only 1.2%. When pelvic lymphadenectomy is compared with pelvic and aortic lymphadenectomy it can be seen that the latter corresponds to a subgroup of higher risk patients in whom radiotherapy was more often administered (52.5% vs 23.8% for patients undergoing only a pelvic lymphadenectomy), this also being reflected in a lower rate of recurrence (3.38% vs 5.9%).

If lymphadenectomy is considered to enable a better selection of at-risk patients, the question which remains to be answered concerns its scope. In their series Mariani *et al.* [24] only performed lymphadenectomy with high-risk patients. None of their patients with a G1 or G2 endometrioid tumour < 2 cm in diameter and < 50% myometrial invasion had node involvement, the five-year survival rate being 100%. This represents 27% of all endometrial cancers [24]. Among high-risk patients there was node involvement in 22%, this being N+ pelvic and N+ aortic in 51% of cases, only N+ pelvic in 33% and only N+ aortic in 16%. Thus, 67% of patients with node dissemination had positive aortic nodes. Moreover, although the appropriate scope of aortic lymphadenectomy had previously been unclear [25, 26] Mariani *et al.* showed that when the aortic result was positive, 77% of nodes were above the mesenteric artery; they thus recommended that paraaortic lymphadenectomy should reach the level of the left renal vein. In our series, 63.6% of patients with positive nodes had aortic involvement, and this was solely aortic in 27.3% of cases. This raises the question as to whether aortic lymphadenectomy should always be performed. Some authors opt for pelvic lymphadenectomy in high-risk patients, and only perform aortic lymphadenectomy when there are positive pelvic nodes. Our data showed that when the pelvic lymphadenectomy was negative, there was aortic involvement in 5.9% of cases. However, 50% of patients with a positive pelvic lymphadenectomy also had aortic involvement. As regards the 84 patients in whom only a pelvic lymphadenectomy was performed it should therefore be assumed that when this was negative (82 cases) the rate of aortic involvement was 5.9%. This corresponds to 4.8 theoretical patients with aortic node involvement. We believe that this number is sufficiently high to suggest that this involvement should not go undetected. At all events it is useful to know the type of any node involvement, since when there is a positive result the likelihood of metastasis is 18.2%, compared with only 2.1% in the absence of nodes. This is also linked to differences in survival, and thus lymphadenectomy is detecting a subgroup of patients at risk of metastasis, on whom efforts should be focused in terms of complementary treatment.

One issue that is considered to be critical [27] is how to select low- and high-risk patients preoperatively. Although Mariani *et al*. [24] report excellent outcomes with preoperative biopsy other authors [28-30] consider that preoperative analysis is less reproducible. One prospective, randomised study found the preoperative and definitive analyses to be correlated in only 67% of cases when assessing myometrial invasion and in only 58% for histological grade, there being overstaging in 18% of patients [30]. This prospective study confirmed previous reports [28-30] regarding the limited agreement between preoperative and definitive analyses. In our centre we demonstrated a positive predictive value of 47% for the absence of invasion, 93% for invasion < 50%, and 92% for invasion > 50%. Therefore, preoperative biopsy based on frozen section is useful to establish whether there is invasion of less than or more than 50%, but it is not very

accurate in terms of diagnosing the type of invasion [31]. This may cease to be a problem under the new FIGO 2009 classification, which does not distinguish between Stage Ia and Ib; Ia now refers to cases of myometrial invasion < 50% and Ib to cases with > 50% [32].

At all events, common sense should be applied. The high rate of comorbidities makes surgery more difficult. In these cases the removal of any suspicious nodes should be mandatory, as around 50% of them will be positive [5, 6]. In the future it is possible that the combination of imaging techniques with determination of the sentinel node will reduce the need for lymphadenectomy without preventing correct staging [33].

Taking the data as a whole we believe that the role of lymphadenectomy remains unclear, although there is evidence to suggest that it helps to target complementary treatment in those patients who might most benefit, as well as selecting subgroups of very high-risk patients. In conclusion, we consider that lymphadenectomy should be performed in high-risk patients, and that it should be a full pelvic and aortic procedure to the level of the left renal vein.

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