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Honing the classification of high-risk endometrial cancer with inclusion of lymphovascular space invasion

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40

41 **HIGHLIGHTS**

- 42 - LVSI status remains a strong prognostic factor in high-risk ECs
- 43 - LVSI could be considered in future trials to guide decision-making in high-risk ECs

44

Abstract

Objectives: The purpose of this study was to analyse the clinical impact of LVSI status in a large French multicentre cohort of women with high-risk ECs according to the ESMO classification.

Methods: Data of 258 women with high-risk EC who received primary surgical treatment between January 2001 and December 2012 were abstracted from prospective multicentre database. The end points were the recurrence and the lymph node metastasis (LNM) rates. Recurrence free survival (RFS) and overall survival (OS) were analyzed.

Results: The recurrence and LNM rates rates in the whole population were 32.9% and 34.5%, respectively. The median follow-up and initial recurrence times were 27 (range: 1–151) and 23.5 (range: 1–151) months, respectively. The respective 3-year RFS rates according to the LNM and LVSI status were, 78.3% (95% CI, 70.1-87.3), 53.7% (95% CI, 40.8-70.6), 65.5% (95% CI, 46.1-93.2), 43.5% (95% CI, 30.3-62.3) for women with no LN metastasis/no LVSI; no LN metastasis/LVSI present; LN metastasis/no LVSI; LN metastasis/ LVSI present, respectively ($p=0.0005$; Figure 1).

Conclusions: LVSI status remains a strong prognostic factor in high-risk ECs associated with a higher recurrence rate and lower RFS and OS whatever the histological type and lymph node status. It could thus be considered in future trials to guide decision-making about adjuvant therapy in high-risk ECs

Introduction:

Endometrial cancer (EC) is the most frequent gynaecological cancer in developed countries and ranks overall as the fourth cancer in women (after breast, lung & bronchus and colon & rectum). The estimated number of new cases in the United States in 2015 was 54 900 with an estimated death rate of 10 200 (7th cancer in terms of lethality) [1, 2]. There were nearly 100 000 newly diagnosed cases in Europe in 2012 with an age standardised incidence of 13.6 per 100 000 women [3].

Most cases of EC are diagnosed at an early stage for which prognosis is very good. However, the European Society for Medical Oncology (ESMO) classification describes a high-risk group with heterogeneous types and grades of EC including endometrioid (type 1), stage IB of the International Federation of Obstetrics and Gynecology (FIGO) classification, grade 3 tumours (type 1/G3ECs), non-endometrioid tumours (type 2) and advanced stages whatever the histological type [3]. These women have a poorer prognosis with an increased risk of metastatic disease and recurrences and represent most of the EC-related deaths. Overall survival and recurrence rates differ widely from one study to another with 5-year survival rates varying between 33 and 79% [4, 5].

Pathological type, myometrial infiltration and nodal status are the three major prognostic factors that are currently used worldwide to standardise treatment strategy, decision-making and clinical trial design for women at high risk [6, 7]. In this specific setting, the lymphovascular space involvement (LVSI) status has been reported as a major prognostic factor [8], especially for the intermediate-risk group, impacting surgical management and indications for adjuvant therapies. However, few data exist about its value in women at high risk for whom the rationale for adjuvant treatment remains somewhat blurred [3, 9–11], especially for women with presumed FIGO stage 1 high-risk EC with no surgical nodal staging or with surgical nodal staging/node negative.

Hence, the purpose of this study was to analyse the clinical impact of LVSI status in a large French multicentre cohort of women with high-risk ECs.

Materials and methods

Study population

Data of women with histologically proven EC defined as high risk according to the ESMO classification [3] (i.e., stage IB, grade 3 with endometrioid type 1; stage I with non-endometrioid type; advanced stages whatever the histological type) who received primary surgical treatment between January 2001 and December 2012 were abstracted from seven institutions with maintained EC databases in France (Tenon University Hospital, Reims University Hospital, Dijon Cancer Center, Rennes University Hospital, Lille University Hospital, Tours University Hospital, and Creteil University Hospital) and from the Senti-Endo trial [12]. All the women had given informed written consent to participate in the study. The research protocol was approved by the Institutional Review Board of the French College of Obstetrics and Gynaecology (CEROG 2014-GYN-020).

All enrolled women underwent preoperative abdomino-pelvic magnetic resonance imaging (MRI) unless contraindicated, in which case a computed tomography (CT) scan was performed. The following clinical, surgical and pathological data were collected: age, body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters), surgical procedure, nodal staging, final pathological analysis (histological type and grade, depth of myometrial invasion, and LVSI status) and adjuvant therapies. All women were classified according to the FIGO 2009 classification [13] after final pathological analysis.

Histological characteristics and ESMO risk groups

In line with the ESMO guidelines, histological type 1 EC includes endometrioid tumours of any histological grade and histological type 2 includes clear cell adenocarcinomas, serous adenocarcinomas and carcinosarcoma [3]. Grade 3 tumours are those with more than 50% of non-squamous, non-morular growth pattern [14]. In addition to the non-squamous solid growth component, a markedly atypical nuclear pattern incongruous for the architectural grade could increase the final tumour grade by one. A tumour is considered LVSI positive when tumour emboli

are found within a space clearly lined by endothelial cells on a haematoxylin and eosin (H&E)-stained section [15].

Treatment and follow-up

Women with histological proven EC had undergone primary surgical treatment including at least total hysterectomy with bilateral salpingo-oophorectomy. Some aspects of the management of high-risk EC changed within the study period: before 2010, nodal staging included pelvic (P-LND) +/- para-aortic lymph node dissection (PA-LND); after 2010, both pelvic and para-aortic lymphadenectomy were recommended. Surgery was performed according to the Institut National du Cancer (INCa) guidelines [14]. Adjuvant therapy was administered on an individual basis at the discretion of a multidisciplinary committee, based on the INCa guidelines and included vaginal brachytherapy (VBT) and/or external beam radiotherapy (EBRT) and/or chemotherapy (CT) and clinical follow-up [16]. Clinical follow-up consisted of physical examinations and the use of imaging techniques according to the findings. Follow-up visits were conducted every 3 months for the first 2 years, every 6 months for the following 3 years, and once a year thereafter.

Recurrence event and recurrence-free survival

Disease recurrence was diagnosed by biopsy or imaging techniques. Time-to-event analyses were calculated from the date of primary surgery as the starting point and women who were alive and without recurrence were censored at the date of last follow-up. Data for survival curves were calculated using the Kaplan–Meier method with log-rank test. Recurrence free survival (RFS) and overall survival (OS) were analyzed. Effects were expressed as hazard ratios with 95% confidence intervals as appropriate. Cox proportional hazard models included established prognostic factors: pathological type, adjuvant therapies, and nodal and LVSI status.

Other analyses

Women, tumour and treatment characteristics were analysed using Chi-square statistics or Fisher's exact test in case of categorical and t-test or analysis of variance (ANOVA) for continuous

144 variables. Values of $P < 0.05$ were considered to denote significant differences. Data were managed
145 with an Excel database (Microsoft, Redmond, WA, USA) and analysed using the R 2.15 software,
146 available online.

147

Results:

Characteristics of the study population

During the study period, 258 women with high-risk EC were documented as having received primary surgical treatment and nodal staging according to the following distribution: Tenon University Hospital (45/258; 17.4%), Tours University Hospital (42/258; 16.3%), Dijon Cancer Center (38/258; 14.7%), Creteil Hospital (33/258; 12.8%), Reims University Hospital (23/258; 9.0%), Rennes University Hospital (26/258; 10.1%), Jeanne de Flandre University Hospital (21/258; 8.1%), and Senti-Endo trial (30/258; 11.6%). The median age of the women was 66.0 years (range 31–91 years) and the BMI 27.7kgm² (range 16.8–50.6). Final histological types 1 and 2 were found in 53.1% (137/258) and 46.9% (121/258) of cases, respectively. The demographics and clinicopathological characteristics of the whole cohort are reported in Table 1. One hundred and twenty-seven women (49.2 %) were found to have LVSI on final histology. Epidemiological, surgical, histological, and outcome characteristics of the women according to LVSI status are reported in Table 2.

Recurrence rate and lymph node metastasis (LNM) rates according to prognostic subgroup

The recurrence rate in the whole population was 32.9% (85/258). When comparing women with and without LVSI, the recurrence rates were 42.5% (54/127) and 23.7% (31/131), respectively (p=0.001).

The LNM rate in the whole population was 34.5% (89/258). When comparing women with and without LVSI, the LNM rates were 52.0% (66/127) and 17.6% (23/131), respectively (p<0.001).

When considering each subgroup according to the LN and LVSI status, the recurrence rates were 22.2% (24/08), 41% (25/61), 30.4% (7/23), 43.9% (29/66), for women with no LN metastasis/no LVSI, no LN metastasis/ LVSI present; LN metastasis/no LVSI, LN metastasis/ LVSI present, respectively (p=0.01).

RFS and OS according to each prognostic subgroup.

The median follow-up and initial recurrence times were 27 (range: 1–151) and 23.5 (range: 1–151) months, respectively.

The respective 3-year RFS rates according to the LVSI status were 76.1% (95% CI, 68.4–84.8) and 45.5% (95% CI, 35.8–57.9) for women with or without LVSI ($p<0.0001$).

The respective 3-year RFS rates according to the LNM and LVSI status were, 78.3% (95% CI, 70.1–87.3), 53.7% (95% CI, 40.8–70.6), 65.5% (95% CI, 46.1–93.2), 43.5% (95% CI, 30.3–62.3) for women with no LN metastasis/no LVSI; no LN metastasis/ LVSI present; LN metastasis/no LVSI; LN metastasis/ LVSI present, respectively ($p=0.0005$; Figure 1).

The 3-year OS for the whole population was 77.8% (95% CI, 58.2–85.8). The respective 3-year OS rates according to the LVSI status were 87.2% (95% CI, 80.8–94.1) and 67.2% (95% CI, 58.1–77.8) ($P<0.0001$) women with or without LVSI.

The respective 3-year OS rates according to the LNM and LVSI status were, 87.3% (95% CI, 80.5–94.7), 70.7% (95% CI, 58.2–85.8), 84.2% (95% CI, 65.3–1), and 64.3% (95% CI, 51.8–79.8) for women with no LN metastasis/no LVSI, no LN metastasis/ LVSI present, LN metastasis/no LVSI, LN metastasis/ LVSI present, respectively ($p=0.0004$).

Treatment

Lymph node dissection (LND) staging

Complete P-PA LND was performed in 28.3 % of the cases. The respective recurrence rates according to complete P-PA LND and P-LND were 34.2% (25/73) and 32.4% (60/185), respectively, ($p=0.8948$). The respective 3-year RFS according to the P-PA-LND and P-LND were 56.5% (95% CI, 43.6–73.3) and 65.7% (95% CI, 58.4–73.8), respectively, ($p=0.276$). The respective 3-year OS rates according to the P-PA-LND and P-LND were 82.6% (95% CI, 72.7–93.9) and 76.6% (95% CI, 70.0–83.9) ($p=0.994$).

Adjuvant therapy

Adjuvant therapy assignment according to LN and LVSI status is reported in figure 3. A significant difference in adjuvant therapy assignment was found depending on the LN and LVSI status ($p < 0.0001$). No difference in adjuvant therapy assignment was found between the two subgroups of women with no LN metastasis/ LVSI present and LN metastasis/no LVSI ($p = 0.2241$).

Multivariate analysis.

In a multivariate analysis including the pathological type, adjuvant therapies, nodal status, and LVSI status we found that adjuvant therapies and LVSI status were independently correlated to 3-year RFS (Table 3).

207 **Conclusion**

208 The results of the current study show that LVSI status remains a strong prognostic factor in
 209 high-risk ECs, independently of histological type and lymph node status. It could thus constitute an
 210 effective tool for identifying a subset of women with poorer prognosis.

211 In the past decade, LVSI status has progressively gained importance as an independent
 212 prognostic factor for women with early-stage EC, especially for women in low- and intermediate-
 213 risk groups [15, 17, 18]. To our knowledge, few data exist on its prognostic value for high-risk ECs
 214 [7, 8, 19]. Furthermore, existing reports are restrictive and conflicting because of sample size,
 215 treatment heterogeneity (indications for nodal staging and adjuvant therapies), and definitions of
 216 risk groups for recurrence [20, 21]. Previous studies have suggested that LVSI status is the strongest
 217 predictor of adverse outcome for both early- (stages I/II disease) and advanced-stage EC (stages
 218 III/IV) [7, 8, 19] and its prognostic value is supported by the current ESMO-ESGO-ESTRO
 219 guidelines [3]. Indeed, a new high-intermediate risk group has been identified and includes women
 220 from the low-intermediate risk group with LVSI [3]. For high-risk ECs, however, the LVSI status is
 221 not used as a prognostic factor and indications for adjuvant therapy are currently exclusively based
 222 on the histological type and FIGO stage (including lymph node status). In the study we report here,
 223 we demonstrate that LVSI status is correlated with the recurrence rate, 3-year RFS and OS,
 224 independently of the LN status. We thus believe that combining LVSI status with existing factors
 225 may identify an additional subset of women with high-risk EC who have poorer prognosis and
 226 require adjuvant therapies [22–24].

227 Several risk classifications for recurrence have been introduced worldwide to standardise
 228 surgical and adjuvant therapeutic management for high-risk ECs [3, 9–11, 25]. However, a debate
 229 about whether type 1/G3ECs should be classified with type 2 ECs as high-risk ECs has been
 230 generated. Several authors justify the inclusion of type 1/G3ECs in the high-risk group due to the
 231 frequency of their coexistence and similarities in clinical characteristics and molecular aspects of

G3EC and type 2 cancers. [20, 22, 26, 27]. While the recent ESMO-ESGO-ESTRO guidelines have validated the incorporation of type 1/G3ECs as high-risk ECs [3], other major classifications [9, 11, 28, 29] used to design clinical trials and adjuvant therapy management exclude the type 1/G3ECs located to corpus uteri from the high-risk group. Hence, indications for treatment strategies differ substantially between authors and countries leading to widely differing practice patterns [3, 9–11, 28]. In the current study, according to European guidelines, we proposed a combination of pathological type 1 and 2 to study the value of LVSI. We found no difference in the recurrence rate and the 3-year RFS between type 1 and 2 high-risk ECs. Moreover, we found that LVSI had the same clinical impact in women at high risk whatever the histological type.

There is a persistent debate about the rationale of pelvic radiotherapy and adjuvant chemotherapy in the standard management of high-risk ECs. In this specific setting, several ongoing clinical trials are assessing the place of chemoradiation, EBRT and chemotherapy alone in high-risk ECs [3]. Although chemotherapy would appear to benefit women at high risk with LNM, its indication in women without LNM is debatable. Indeed, the ESMO-ESGO-ESTRO guidelines recently recommended the following approach for women with type 1 high-risk EC with negative nodal staging: (i) adjuvant EBRT to decrease loco-regional recurrence, (ii) adjuvant brachytherapy as an alternative to decrease vaginal recurrence and (iii) adjuvant systemic therapy (currently under investigation). However, these guidelines do not take the LVSI status into account [3]. In the current study, we hypothesized that the management of women at high risk but without LNM could be improved by including the LVSI status. We found that LVSI may be a major prognostic factor for this subgroup of women, as women who were LVSI positive/node negative had a poorer prognosis than those with nodal metastases. Such differences could be explained by either the LVSI status itself or the lower rate of assignment of adjuvant therapies (especially chemotherapy) for women who were LVSI positive/node negative. Future trials evaluating the place of adjuvant chemotherapy for this subgroup of women should therefore consider the LVSI status as a decision

criterion. Another situation concerns women with type 1 high-risk EC without nodal staging (either because of discrepancies between preoperative and final histology or because the woman was unable to undergo complete nodal staging due to multiple comorbidities) [30, 31]. For these women, adjuvant EBRT is recommended, while sequential adjuvant chemotherapy could be an option [3]. Here again, LVSI status may be a good tool to select women for chemotherapy. Finally, for women who have high-risk type 2 EC (serous and clear cell adenocarcinoma) and are node negative, the place of adjuvant chemotherapy remains uncertain (level of evidence III) [3]. Although LVSI status is considered for women with stage IA this is not the case for those with stage IB. Once again, for this subgroup of women, we found a lower RFS and OS when the LVSI was positive implying that adjuvant chemotherapy could be important even in the absence of LNM.

Several limits of the study deserve to be mentioned. First, we cannot exclude bias linked to its retrospective nature. Second, the median follow-up for recurrence was relatively short. However, the majority of recurrences (74%; 63/85) occurred during the two 2 years of follow up. In addition, our median time of follow up is consistent with previous studies evaluating the prognosis of high-risk ECs [22–24]. Third, during the data collection period, modifications occurred in staging modalities (FIGO classification), and the indications for nodal staging and for adjuvant therapies. In the current study only 28.3% underwent a P-PA LND, while a P-LND was performed in all cases. This low rate can be explained by: i) PA -LND was not systematically recommended in France for high-risk patients before 2010; ii) patients in whom there was a discrepancy between pre- and postoperative risk groups did not systematically undergo secondary PA-LND, mainly due to associated morbidities [32]. However, we found no improvement in the survival rates between women who underwent complete nodal staging and those who underwent exclusive P-LND.

LVSI appears to be a major prognostic factor in high-risk ECs associated with a higher recurrence rate and lower RFS and OS whatever the histological type. LVSI should be considered in future trials to guide decision-making about adjuvant therapy in high-risk ECs, whatever the

282 histological type or nodal status.

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285 **Conflict of interest statement**

286 No authors have conflict of interests.

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Figures legends

Figure 1: Recurrence-free survival according to prognostic sub-group in the whole cohort

($p=0.0005$)

Figure 2: Recurrence-free survival according to prognostic sub-group for type 1 EC

($p=0.0006$)

Figure 3: Flow chart according to LVSI and lymph node status

Table 1: Characteristics of the whole population

Characteristics	Population % (n) n=258
Age -median (range)	66.0 y (range 31-91)
BMI -median (range)	21,9 y (range: 17-50,6)
Follow-up (months)-median(range)	27 (range: 1-151)
Histological type %(n)	
- Type 1	53.1% (137)
- Type 2	46.9% (121)
Nodal staging -n(%)	
- P-LND	100%
- PPA-LND	28.3%
FIGO stage at definitive histology %(n)	
- I	34.1%(88)
- II	16.3%(42)
- III	49.6%(128)
Adjuvant therapies %(n)	
- No adjuvant therapy	7%(17)
- Vaginal brachytherapy alone	12%(32)
- EBRT +/- brachytherapy	31%(79)
- Chemotherapy +/- EBRT	50%(130)
Outcomes %(n)	
- Recurrence	32.9% (85)
- Lymph node metastasis	34.5% (89)

P-PA-LND : Pelvic / para-aortic Lymph Node Dissection, EBRT : external beam radiotherapy

Table 2: Comparison of epidemiological, surgical and histological characteristics of patients with and without LVSI at final histology.

	No LVSI n=131 n (%)	LVSI n=127 n (%)	p value
Age -median (range)	64.8 (31-91)	68.0 (44-88)	0.11
BMI -median (range)	27.2 (17- 50.6)	26.1 (16.7- 48.4)	0.03
Follow-up (months)- median(range)	31 (1-151)	23.5 (1-116)	0.008
Histological type n(%)			
- Type 1	77 (58.8)	60 (47.2)	0.0834
- Type 2	54 (41.2)	67 (52.8)	
Nodal staging -n (%)			
- P-PA-LND	26 (19.8)	47 (37.0)	0.0034
- P-LND	105 (80.2)	80 (63.0)	
Nodal metastases -n(%)	23 (17.6)	66 (52.0)	<0.0001
Adjuvant therapies n(%)			
- No adjuvant therapy	13 (9.9)	4 (3.1)	0.0006
- Vaginal brachytherapy	24 (18.3)	8 (6.3)	
- EBRT +/- brachytherapy	41 (31.3) 53 (40.5)	38 (30) 77 (60.6)	
- Chemotherapy +/- EBRT			
Recurrences -n(%)	31 (23.7)	54 (42.5)	0.0020

Table 3: Multivariate analysis of recurrence-free survival.

Covariates	RFS	
	HR 95%CI	P
Adjuvant therapies		
- Vaginal brachytherapy	Reference	
- Chemotherapy +/- EBRT	4.08 (1.22-13.60)	0.0218
- EBRT +/- brachytherapy	5.27 (1.59-17.46)	0.0065
- No adjuvant therapy	4.39 (1.02-18.82)	0.0461
LVSI status		
- No	Reference	
- Yes	2.07 (1.27-3.34)	0.0032
Lymph node status		
- No metastasis	Reference	
- Metastasis	1.12 (0.69-1.81)	0.6446
Pathological types		
- Type 1	Reference	
- Type 2	1.20 (0.76-1.87)	0.4220

Figure 1: Recurrence-free survival according to prognostic sub-group in the whole cohort ($p=0.0005$)

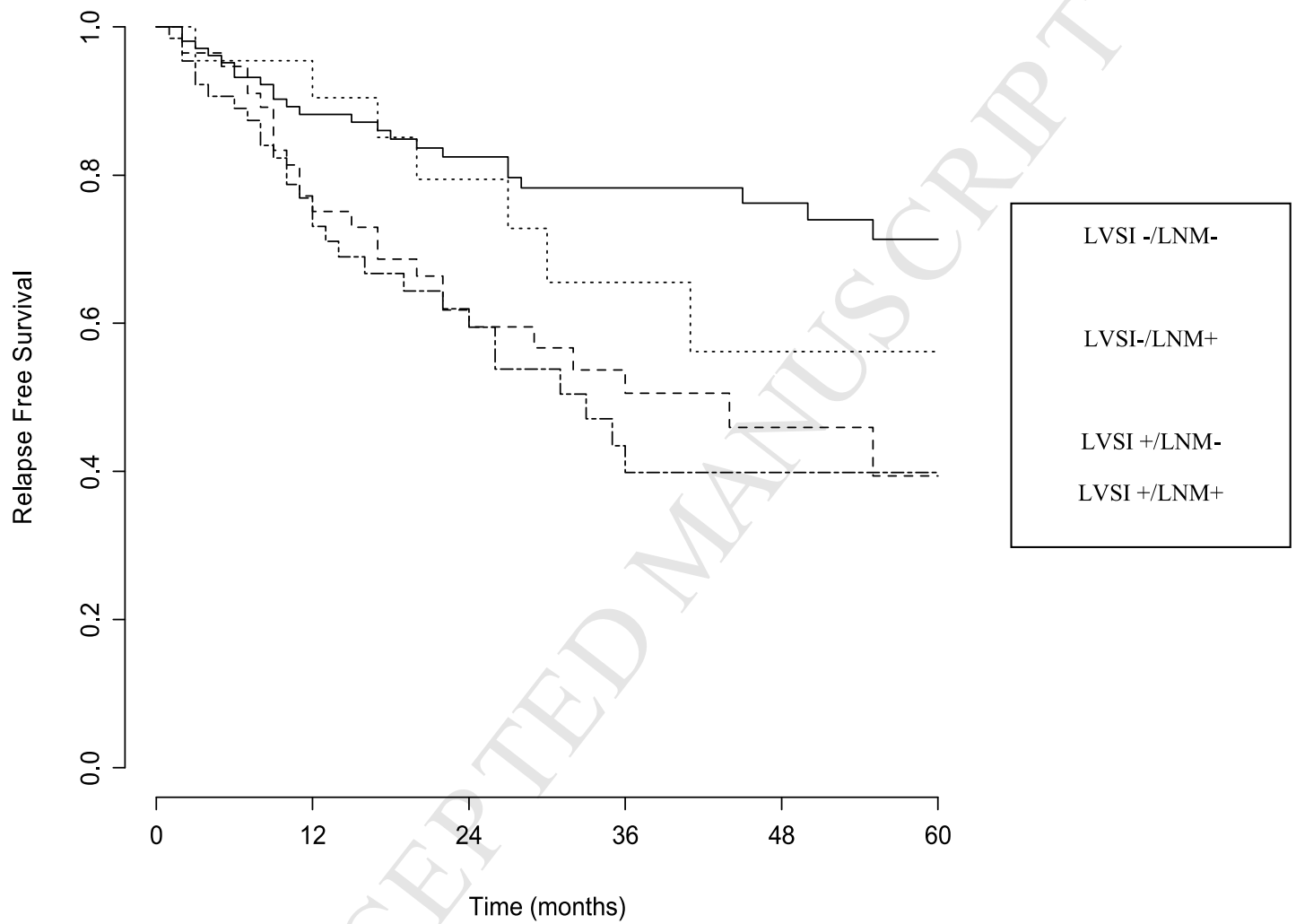


Figure 2: Recurrence-free survival according to prognostic sub-group for type 1 EC (p=0.0006)

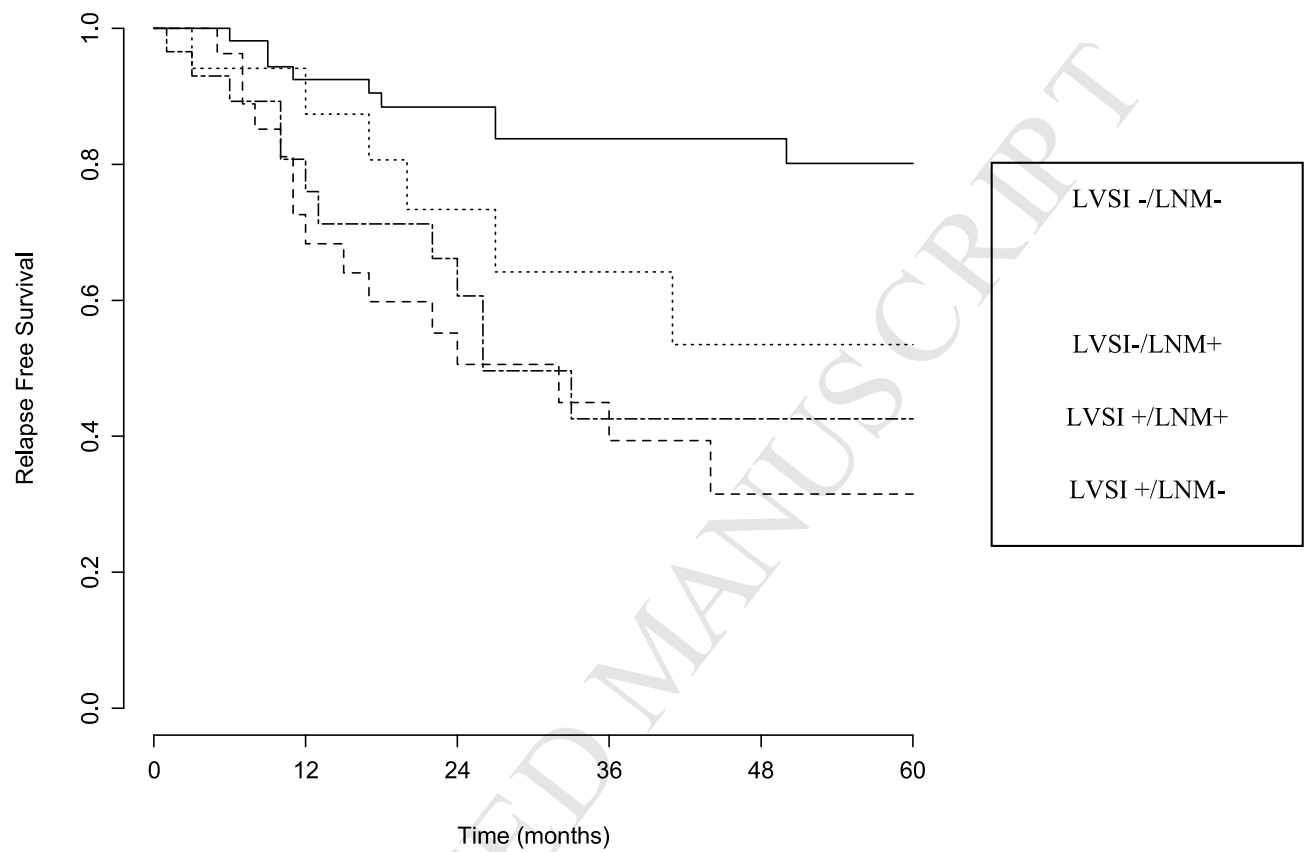


Figure 3: Flow chart according to LVSI and lymph node status

