# Progesterone Receptor Expression Is an Independent Prognosticator in FIGO Stage I Uterine Leiomyosarcoma

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**Key Words:** Uterine sarcoma; Hormone receptors; Immunohistochemistry; Survival

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## ABSTRACT

***Objectives:*** *To analyze the clinical role of hormone receptors in a large uterine sarcomas series with long-term follow-up.*

***Methods:*** *Protein expression of estrogen receptor (ER) and progesterone receptor (PR) by immunohistochemistry was studied in tissue microarrays from 294 patients diagnosed with uterine sarcoma in Norway from 1970 to 2000 and analyzed for an association with clinicopathologic parameters and outcome.*

***Results:*** *ER and PR were detected in 136 of 291 and 184 of 291 tumors (three noninformative cases each), respectively. Expression was unrelated to histology, patient age, tumor diameter, the degree of atypia, the presence of necrosis or vascular invasion, or mitotic counts. ER and PR expression was unrelated to survival in the analysis of the entire cohort. When survival analysis was confined to stage I leiomyosarcoma ($n = 147$), higher PR score was significantly related to longer overall survival (OS) ($P = .042$). Clinicopathologic prognosticators in this group were age ($P = .041$), tumor diameter ($P = .001$), and mitotic count ($P = .007$), with a trend for atypia ($P = .087$). In Cox multivariate analysis, PR score ($P = .019$), tumor diameter ($P = .013$), and mitotic count ($P = .002$) were independent prognosticators of OS.*

***Conclusions:*** *Hormone receptor expression is not informative of outcome in the analysis of uterine sarcomas of all stages and histologic types. PR expression identifies patients with longer survival in stage I leiomyosarcoma.*

CME/SAM

Upon completion of this activity you will be able to:
- discuss the histology of uterine sarcoma.
- compare hormone receptor expression across different histologic types of uterine sarcoma.
- comment on the prognostic role of clinicopathologic parameters and hormone receptors in uterine sarcoma.

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Uterine sarcomas are rare tumors, comprising 7% of all soft tissue sarcomas and 3% of uterine malignancies.[1,2] In a retrospective study of all sarcomas in Norway from 1970 to 2000 from our institution, uterine sarcomas comprised 419 (3.4%) of 12,431 uterine malignancies.[3] Leiomyosarcoma (LMS) and endometrial stromal sarcoma (ESS) are the most common histologic types.[2,3] Adenosarcoma and carcinosarcoma are both recognized as mixed epithelial-mesenchymal tumors. However, only the former have a true sarcomatous component, whereas carcinosarcomas are now regarded as metaplastic carcinomas. ESS, previously classified as low grade or high grade and subsequently regarded as a single entity, was recently redivided into low-grade and high-grade categories, although the latter group constitutes rare tumors.[4]

Hormone receptor inhibition is used as a therapeutic modality for some patients with uterine sarcoma, particularly

those with recurrent or metastatic ESS,[2,5] and was recently suggested to be useful for the treatment of advanced hormone receptor–positive LMS.[6] However, the clinical role of estrogen receptor (ER) and progesterone receptor (PR) expression in uterine sarcoma has not been fully established to date. Several studies applying immunohistochemistry (IHC) have analyzed the prognostic role of ER and PR in these tumors.[7-14] However, most of these studies[7-12] included fewer than 50 cases, and the largest analyzed 100 tumors. The material analyzed in some of these studies consisted exclusively of LMS, while other studies included uterine sarcomas of different histology. Carcinosarcomas—tumors that, as discussed above, are to date not considered true sarcomas—were included in three of these studies.[12-14]

Our group previously published a population-based study of 419 uterine sarcomas diagnosed in Norway from 1970 to 2000.[3] This analysis identified several clinicopathologic parameters with a prognostic role in these tumors. However, crude rather than disease-specific survival was used as the end point. In the present study, we analyzed the clinical role of ER and PR in 294 of the above-mentioned 419 uterine sarcomas from patients for whom disease-specific survival was available as an end point, in what constitutes, to our knowledge, the largest study dealing with the clinical role of ER and PR in uterine sarcoma to date.

## Materials and Methods

### Patients and Materials

Specimens consisted of 294 tumors from patients diagnosed with uterine sarcoma in Norway from 1970 to 2000. Diagnoses were established based on morphology and IHC by an experienced gynecologic pathologist (V.M.A.) following review of this series.[3,15] Tissue microarrays (TMAs) were constructed using three to four 0.6-mm punch biopsy specimens from each of the primary uterine tumors. Clinicopathologic data are shown in **Table 1**. Clinical data were from the Department of Gynecologic Oncology at the Norwegian Radium Hospital. None of the patients received antihormonal therapy.

The study was approved by the Regional Committee for Medical Research Ethics in Norway.

### IHC

Formalin-fixed, paraffin-embedded sections from five TMA slides were analyzed for ER and PR protein expression using the Dako EnVision Flex+ System (K8012; Dako, Glostrup, Denmark). Deparaffinization and unmasking of epitopes were carried out in a PT-Link (Dako) using an EnVision Flex target retrieval solution at high pH (Tris/EDTA pH 10). Sections were incubated with a 0.3% hydrogen peroxide ($H_2O_2$) solution for 5 minutes to block endogenous tissue peroxidase activity. Sections were incubated with a mouse immunoglobulin G1 (IgG1) ER antibody, clone 6F11, at 1:200 dilution, and a mouse IgG1 PR antibody, clone 1A6, used at 1:300 dilution, both from Novocastra (Newcastle-upon-Tyne, UK), and then treated with EnVision Flex+ mouse linker (15 minutes) and EnVision Flex/HRP enzyme (30 minutes). Sections were stained for 10 minutes with 3′3-diaminobenzidine tetrahydrochloride, counterstained with hematoxylin, dehydrated, and mounted in Richard-Allan Scientific Cyto seal XYL (Thermo Fisher Scientific, Waltham, MA). Positive controls consisted of a breast carcinoma and uterine carcinoma for ER and PR, respectively. Negative controls

**Table 1**
**Clinicopathologic Parameters of the Study Cohort (294 Patients)[a]**

| Parameter | Value |
|---|---|
| Age, mean (range), y | 58 (20-90) |
| Histologic type | |
| Leiomyosarcoma[b] | 187 |
| Endometrial stromal sarcoma[c] | 64 |
| Adenosarcoma | 16 |
| High-grade endometrial sarcoma | 13 |
| Sarcoma, NOS | 7 |
| Other[d] | 7 |
| Tumor diameter, cm | |
| ≤10 | 217 |
| >10 | 63 |
| NA | 14 |
| Atypia | |
| Mild | 83 |
| Moderate | 112 |
| Severe | 93 |
| NA | 6 |
| Mitotic count (10 high-power fields) | |
| ≤10 | 174 |
| >10 | 118 |
| NA | 2 |
| Necrosis | |
| Absent | 68 |
| Present | 222 |
| NA | 4 |
| Vascular invasion | |
| Absent | 152 |
| Present | 126 |
| NA | 16 |
| Extrauterine disease at diagnosis | |
| Absent | 227 |
| Present | 67 |

NA, not available; NOS, not otherwise specified.
[a]Values are presented as number of patients unless otherwise indicated.
[b]Including 15 myxoid and three epithelioid leiomyosarcomas.
[c]Low-grade endometrial stromal sarcoma according to the World Health Organization 2014 classification.
[d]Including three rhabdomyosarcomas, three giant cell sarcomas (two combined with leiomyosarcoma, one combined with sarcoma NOS), and one perivascular epithelioid cell tumor.




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were stained with nonrelevant mouse antibody of the same isotype.

*IHC Scoring*

Staining extent and intensity were scored separately by two experienced gynecologic pathologists (V.M.A. and B.D.). Tumors were scored as negative (0% stained cells), focally positive (1%-10% stained cells), moderately positive (11%-50% stained cells), or diffusely positive (staining in >50% cells), corresponding to a score of 0 to 3, and as negative, weakly stained, or strongly stained, corresponding to a score of 0 to 2. Multiplying the two values generated a combined score of 0 to 6, which was used in the statistical analysis. Discordant cases were discussed in consensus sessions until agreement was reached.

### Statistical Analysis

Statistical analysis was performed applying the SPSS-PC package (version 21; SPSS, Chicago, IL). A probability of less than .05 was considered statistically significant. Analysis of the association between protein expression and clinicopathologic parameters was performed using the Mann-Whitney *U* test or the Kruskal-Wallis *H* test depending on the number of groups (two vs three or more, respectively). For this analysis, as well as for survival analysis, clinicopathologic parameters were grouped as follows: age, 60 years or younger vs older than 60 years; histology, LMS vs ESS vs adenosarcoma vs high-grade endometrial sarcoma vs other sarcomas vs sarcoma, not otherwise specified; tumor diameter, 10 cm or less vs more than 10 cm; mitotic count, 10 or less vs more than 10; atypia, mild vs moderate vs severe; necrosis, yes vs no; vascular invasion, yes vs no; and disease extent, confined to uterus vs disease outside the uterus. The association between hormone receptor expression and survival was assessed using two cutoffs: negative vs positive staining (any extent and intensity) and low (combined score 0-3) vs high (combined score 4-6) staining.

Overall survival (OS) was calculated from the date of surgery to last follow-up. Univariate survival analyses were executed using the Kaplan-Meier method and log-rank test. Multivariate analysis was performed using the Cox regression model (Enter function).

Relapse-free survival was not analyzed due to incomplete data.

## Results

The five TMA blocks contained a total of 1,063 cores from the previously studied uterine sarcoma cohort of 419 patients.[3] Of these, 825 cores were from the 294 tumors studied in the present report, with the following distribution: three informative cores were available from 251 tumors, two from 29 tumors, and one from 14 tumors. These 814 cores were informative for at least one antibody, the majority (>95%) for both ER and PR.

Representative examples of ER and PR immunostaining are shown in **Image 1**. Interobserver agreement was more than 80%, with most discordant cases being at one scoring level and easily settled at consensus sessions. Staining was observed in some tumors within each of the six diagnostic categories, with no significant differences observed in ER or PR intensity and extent or in the combined staining score **Table 2** and **Table 3**. Different cores from the same tumor often, although not always, had the same staining extent and intensity (Supplementary Table 1; all supplemental materials can be found at *American Journal of Clinical Pathology* online). ER and PR expression score was similarly unrelated to patient age, tumor diameter, the degree of atypia, the presence of necrosis or vascular invasion, and mitotic count ($P > .05$; data not shown).

In subgroup analysis of LMS, higher PR score was positively related to the presence of tumor necrosis ($P = .038$), with no other significant associations for ER or PR score. In analysis limited to ESS, higher PR score was related to lower tumor diameter ($P = .022$), with no other statistically significant findings.

The follow-up period for the 294 patients ranged from 0 to 430 months. At the last follow-up, 77 patients were alive with no evidence of disease, 189 were dead of disease, and 28 were dead of other causes. Mean and median OS were 92 and 60 months, respectively.

Survival analyses were performed for the entire cohort (291 patients with data for ER and 291 with data for PR), as well as separately for patients with ESS and LMS. ER and PR score was unrelated to OS ($P > .05$; data not shown). ER expression, categorized as yes vs no, was associated with a trend for longer OS for ER-expressing tumors ($P = .079$), with no relationship observed for PR ($P = .425$). Separate analysis of the prognostic role ER and PR staining extent and intensity separately similarly failed to show any significant association with disease outcome ($P > .05$; data not shown). In contrast, strong association was observed between OS and patient age ($P = .001$), the presence of extrauterine disease ($P < .001$), histology ($P < .001$), tumor diameter ($P = .002$), atypia ($P < .001$), mitotic count ($P < .001$), and the presence of necrosis ($P = .001$; **Figure 1**). The presence of vascular invasion was unrelated to OS ($P = .64$; data not shown).

In Cox multivariate analysis, disease extent ($P < .001$), patient age ($P = .003$), histology ($P = .028$), and mitotic count ($P < .001$) were independent prognosticators of OS.







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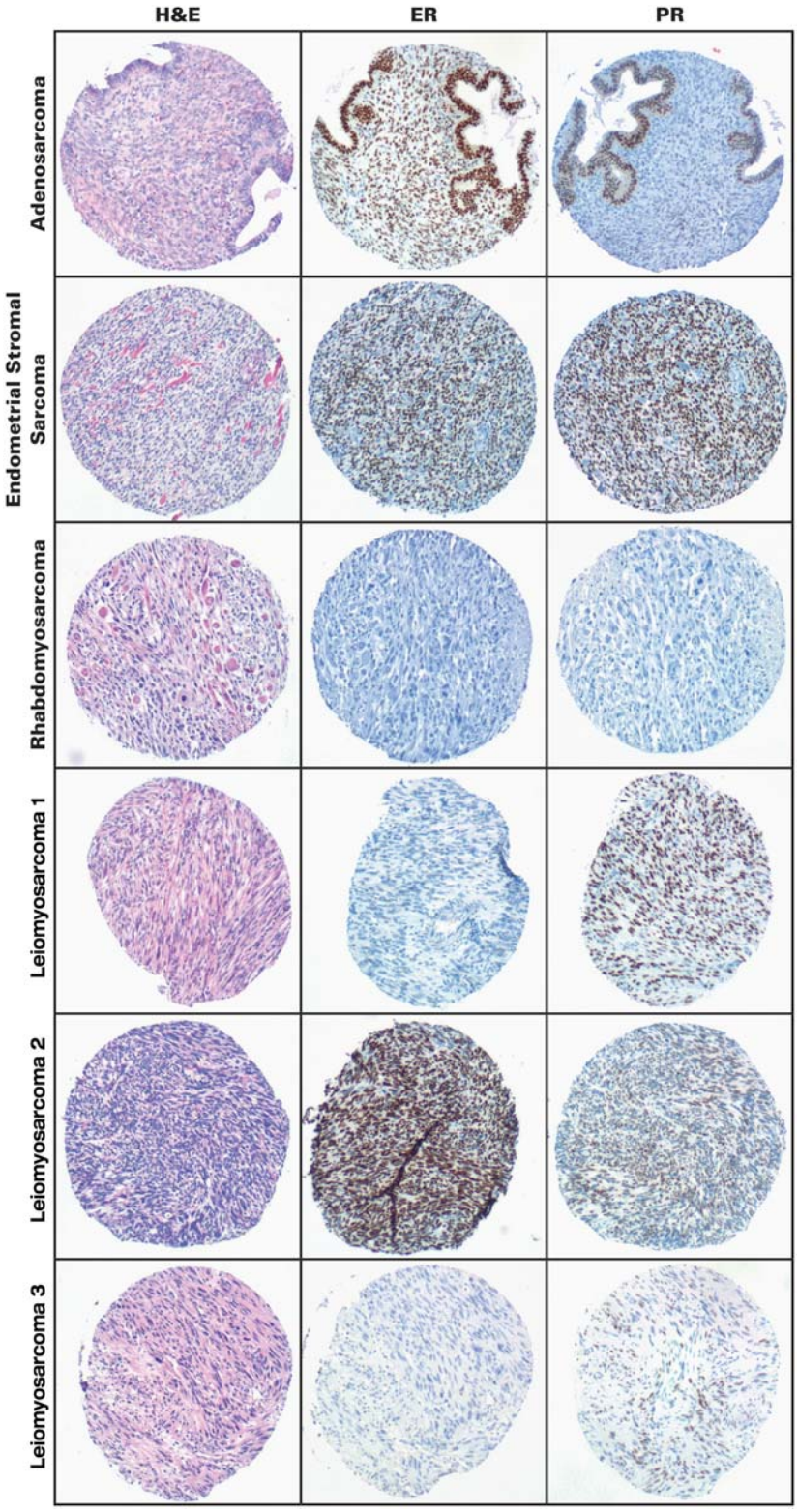


**Image 1** Representative examples of estrogen receptor (ER) and progesterone receptor (PR) expression by immunohistochemistry in uterine sarcoma. Adenosarcoma: diffuse strong stain for ER in tumor cells, as well as in the benign epithelial cells. Tumor cells are PR negative, whereas epithelial cells (not scored) are PR positive. Endometrial stromal sarcoma: there is diffuse strong staining for ER and PR. Rhabdomyosarcoma: there is negative staining for ER and PR. Leiomyosarcoma 1: there is a negative ER stain and strong PR expression in more than 50% of tumor cells, scored as diffuse. Leiomyosarcoma 2: there is a strong diffuse ER stain and weak diffuse PR expression. Leiomyosarcoma 3: there is a negative ER stain and weak PR expression in less than 50% of tumor cells.




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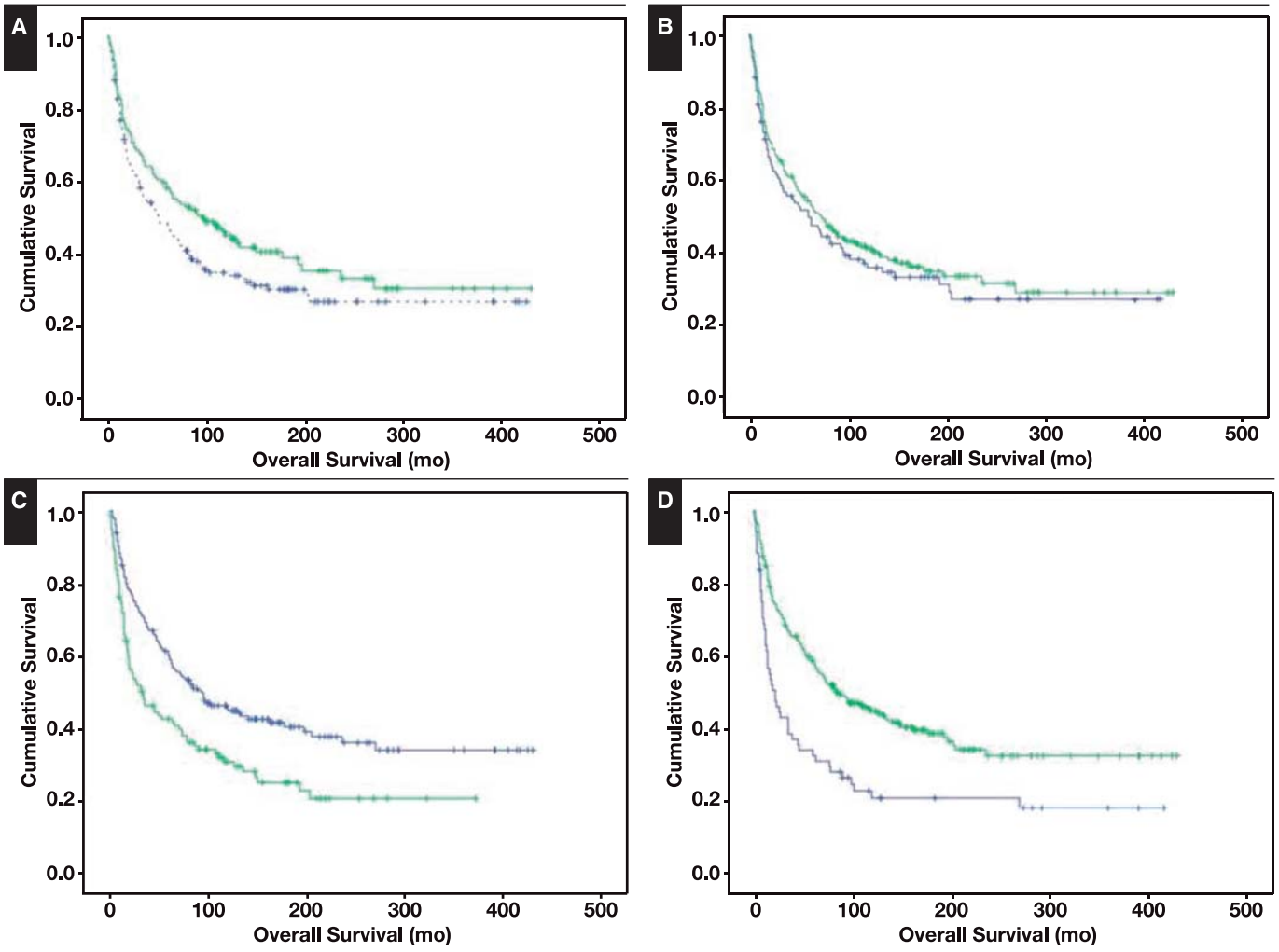


**Figure 1** Clinicopathologic parameters, but not estrogen receptor (ER) and progesterone receptor (PR) expression, are informative of clinical outcome in uterine sarcoma of all stages and histologic types. **A**, ER score: Kaplan-Meier survival curve showing the trend for association between ER protein expression and overall survival (OS) for patients with uterine sarcoma (n = 291; three patients with noninformative tumors). Patients with ER-expressing tumors (n = 136, green line) had a median OS of 95 months vs 51 months for patients with ER-negative tumors (n = 155, blue line; $P = .079$). **B**, PR score: Kaplan-Meier survival curve showing the lack of association between PR protein expression and OS for patients with uterine sarcoma (n = 291; three patients with noninformative tumors). Patients with PR-expressing tumors (n = 184, green line) had a median OS of 71 months vs 60 months for patients with PR-negative tumors (n = 107, blue line; $P = .425$). **C**, Age: Kaplan-Meier survival curve showing the association between patient age and OS for patients with uterine sarcoma (n = 294). Patients 60 years or younger (n = 178, blue line) had a median OS of 89 months vs 32 months for patients older than 60 years (n = 116, green line; $P = .001$). **D**, Disease extent: Kaplan-Meier survival curve showing the association between the presence of extrauterine disease and OS for patients with uterine sarcoma (n = 294). Patients with tumors confined to the uterus (n = 227, green line) had a median OS of 84 months vs 22 months for patients with extrauterine disease (n = 67, blue line; $P < .001$).

In survival analysis limited to LMS, a trend was observed between higher PR score and longer OS ($P = .087$; data not shown). No association with survival was observed for ER score or for ER and PR scored as yes vs no. Subgroup analysis of ESS did not show any association between ER or PR (score or categorical yes vs no value) and OS.

Survival analysis was subsequently performed for patients with disease limited to the uterus (n = 227). Neither ER nor PR (score or yes vs no) was related to OS in this group. ER and PR staining extent and intensity analyzed separately were similarly unrelated to OS ($P > .05$; data not shown).

When analysis was confined to stage I LMS (n = 147; three patients with noninformative tumors), an association was seen between higher PR score and longer OS ($P = .042$). Strong staining intensity for PR, irrespective of staining extent, was similarly significantly related to longer OS ($P = .014$) **Figure 2**, with no such role for PR staining extent







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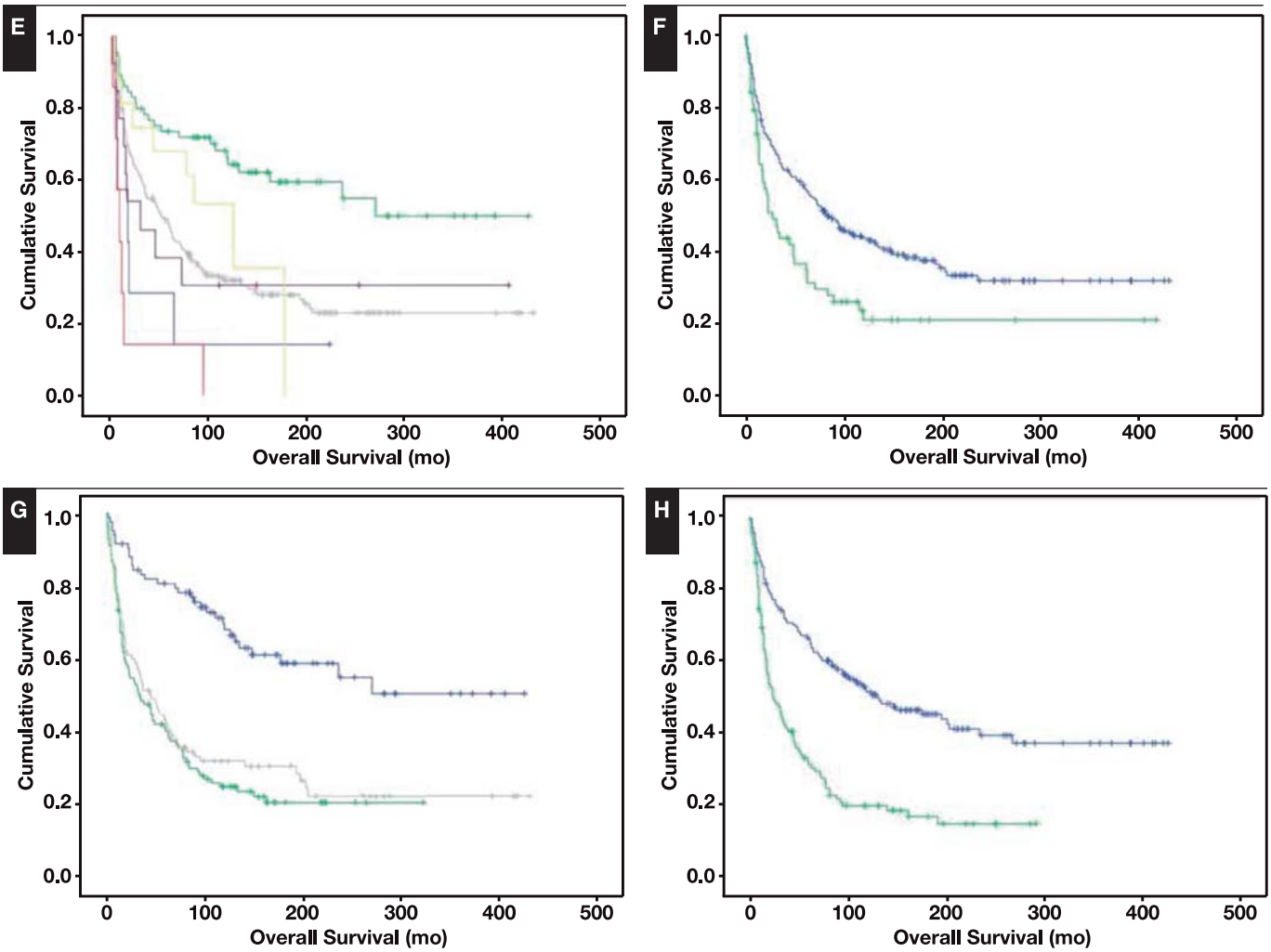


**Figure 1** (cont) **E**, Histology: Kaplan-Meier survival curve showing the association between histology and OS for patients with uterine sarcoma (n = 294). Patients with endometrial stromal sarcoma (n = 64, green line) had a median OS of 270 months vs 126 months for patients with adenosarcoma (n = 16, yellow line); 52 months for patients with leiomyosarcoma (n = 187, gray line); 31 months for patients with high-grade endometrial sarcoma (n = 16, purple line); 10 months for patients with sarcoma, not otherwise classified (n = 7, red line); and 18 months for patients with other sarcomas (n = 7, blue line; $P < .001$). **F**, Tumor diameter: Kaplan-Meier survival curve showing the association between the tumor diameter and OS for patients with uterine sarcoma (n = 280; 14 patients with missing data). Patients with tumors measuring 10 cm or less (n = 217, blue line) had a median OS of 84 months vs 28 months for patients with extrauterine disease (n = 63, green line; $P = .002$). **G**, Atypia: Kaplan-Meier survival curve showing the association between the degree of atypia and OS for patients with uterine sarcoma (n = 288; six patients with missing data). Patients with tumors with mild atypia (n = 83, blue line) had a median OS of 270 months vs 33 and 44 months for those with tumors that had moderate (n = 112, green line) or severe (n = 93, gray line) atypia, respectively ($P < .001$). **H**, Mitotic count: Kaplan-Meier survival curve showing the association between the mitotic count and OS for patients with uterine sarcoma (n = 292; two patients with missing data). Patients with tumors that had 10 or fewer mitoses per 10 high-power fields (n = 174, blue line) had a median OS of 131 months vs 23 months for those with tumors having more than 10 mitoses per 10 high-power fields (n = 118, green line; $P = .002$).

($P = .178$). Clinicopathologic prognosticators in this group were patient age ($P = .041$), tumor diameter ($P = .001$), and mitotic count ($P = .007$), with a trend for the degree of atypia ($P = .087$; Figure 2). The presence of necrosis ($P = .306$) and vascular invasion ($P = .245$) was unrelated to survival in this patient group (data not shown). In Cox multivariate analysis, PR score ($P = .019$), tumor diameter ($P = .013$), and mitotic count ($P = .002$) were independent prognosticators of OS. When PR score was replaced by PR staining intensity in the Cox analysis, PR staining intensity ($P = .043$), tumor diameter ($P = .011$), and mitotic count ($P = .003$) were independent prognosticators of OS.




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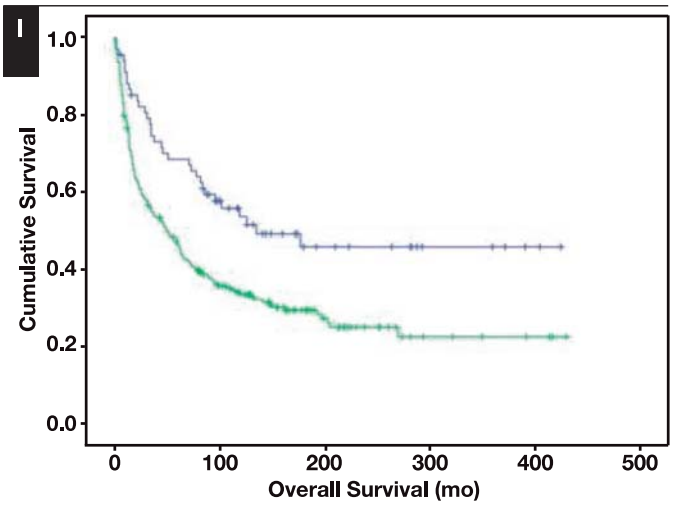


**Figure 1** (cont) I, Necrosis: Kaplan-Meier survival curve showing the association between the presence of necrosis and OS for patients with uterine sarcoma (n = 290; four patients with missing data). Patients with tumors with no necrosis (n = 68, blue line) had a median OS of 135 months vs 50 months for patients with tumors with necrosis (n = 222, green line; $P = .001$).

**Table 2**
**ER and PR Extent in Uterine Sarcomas of Different Histology (n = 291)[a]**

| | Staining Extent Score | | | | |
|---|---|---|---|---|---|
| **Parameter/Tumor Type** | **0** | **1** | **2** | **3** | **Total** |
| ER extent | | | | | |
| Leiomyosarcoma[b] | 102 | 24 | 16 | 43 | 185 |
| Endometrial stromal sarcoma[c] | 30 | 8 | 6 | 20 | 64 |
| Adenosarcoma | 6 | 4 | 2 | 4 | 16 |
| High-grade endometrial sarcoma | 10 | 0 | 3 | 0 | 13 |
| Sarcoma NOS | 3 | 1 | 1 | 2 | 7 |
| Other[d] | 4 | 0 | 0 | 2 | 6 |
| PR extent | | | | | |
| Leiomyosarcoma[b] | 65 | 25 | 20 | 74 | 184 |
| Endometrial stromal sarcoma[c] | 21 | 14 | 9 | 20 | 64 |
| Adenosarcoma | 6 | 4 | 1 | 5 | 16 |
| High-grade endometrial sarcoma | 9 | 0 | 2 | 2 | 13 |
| Sarcoma NOS | 3 | 0 | 1 | 3 | 7 |
| Other[d] | 3 | 0 | 0 | 4 | 7 |

ER, estrogen receptor; NOS, not otherwise specified; PR, progesterone receptor.
[a]Three noninformative cases each for ER and PR.
[b]Including 15 myxoid and three epithelioid leiomyosarcomas.
[c]Low-grade endometrial stromal sarcoma according to the World Health Organization 2014 classification.
[d]Including three rhabdomyosarcomas, three giant cell sarcomas (two combined with leiomyosarcoma, one combined with sarcoma NOS), and one perivascular epithelioid cell tumor.

## Discussion

Uterine sarcomas, particularly LMS, have the propensity to metastasize and are associated with significant morbidity and mortality. As uterine sarcomas respond in general less favorably to chemotherapy and radiotherapy compared with carcinomas, germ cell tumors, and hematologic cancers, there is an obvious need to identify candidate molecules for targeted therapy for this patient group.

We previously reported on differences in the gene expression profiles of LMS vs ESS.[16] Hormone receptor genes were not among the differentially expressed molecules, suggesting they have no applicability as diagnostic markers used to differentiate between the various types of uterine sarcoma. The present study supports this observation, as ER and PR were expressed in all types of uterine sarcoma, including unclassifiable ones and rare, clinically aggressive entities. The fact that approximately 50% of tumors express hormone receptors does, however, reinforce the rationale of blocking these receptors as a therapeutic modality in recurrent and/or metastatic disease.

In the present study, ER and PR had no prognostic role in the analysis of the entire cohort, in which clinicopathologic parameters, including age, disease stage, histology, tumor diameter, the degree of atypia, mitotic count, and the presence of necrosis, were powerful prognosticators, the majority also in multivariate analysis. The prognostic relevance of these parameters is well in agreement with previous data for the entire Norwegian sarcoma series using crude survival as the end point.[3] ER and PR expression was similarly noninformative for outcome in separate analyses of LMS and ESS at all International Federation of Gynecology and Obstetrics (FIGO) stages, as well as in analysis to stage I sarcomas of all histologic types. However, higher PR score was significantly related to longer OS in

**Table 3**
**ER and PR Intensity in Uterine Sarcomas of Different Histology (n = 291)[a]**

| | Staining Intensity Score | | | |
|---|---|---|---|---|
| **Parameter/Tumor Type** | **0** | **1** | **2** | **Total** |
| ER intensity | | | | |
| Leiomyosarcoma[b] | 102 | 45 | 38 | 185 |
| Endometrial stromal sarcoma[c] | 30 | 15 | 19 | 64 |
| Adenosarcoma | 6 | 6 | 4 | 16 |
| High-grade endometrial sarcoma | 10 | 3 | 0 | 13 |
| Sarcoma NOS | 3 | 2 | 2 | 7 |
| Other[d] | 4 | 0 | 2 | 6 |
| PR intensity | | | | |
| Leiomyosarcoma[b] | 65 | 27 | 92 | 184 |
| Endometrial stromal sarcoma[c] | 21 | 13 | 30 | 64 |
| Adenosarcoma | 6 | 2 | 8 | 16 |
| High-grade endometrial sarcoma | 9 | 0 | 4 | 13 |
| Sarcoma NOS | 3 | 1 | 3 | 7 |
| Other[d] | 3 | 0 | 4 | 7 |

ER, estrogen receptor; NOS, not otherwise specified; PR, progesterone receptor.
[a]Three noninformative cases each for ER and PR.
[b]Including 15 myxoid and three epithelioid leiomyosarcomas.
[c]Low-grade endometrial stromal sarcoma according to the World Health Organization 2014 classification.
[d]Including three rhabdomyosarcomas, three giant cell sarcomas (two combined with leiomyosarcoma, one combined with sarcoma NOS), and one perivascular epithelioid cell tumor.





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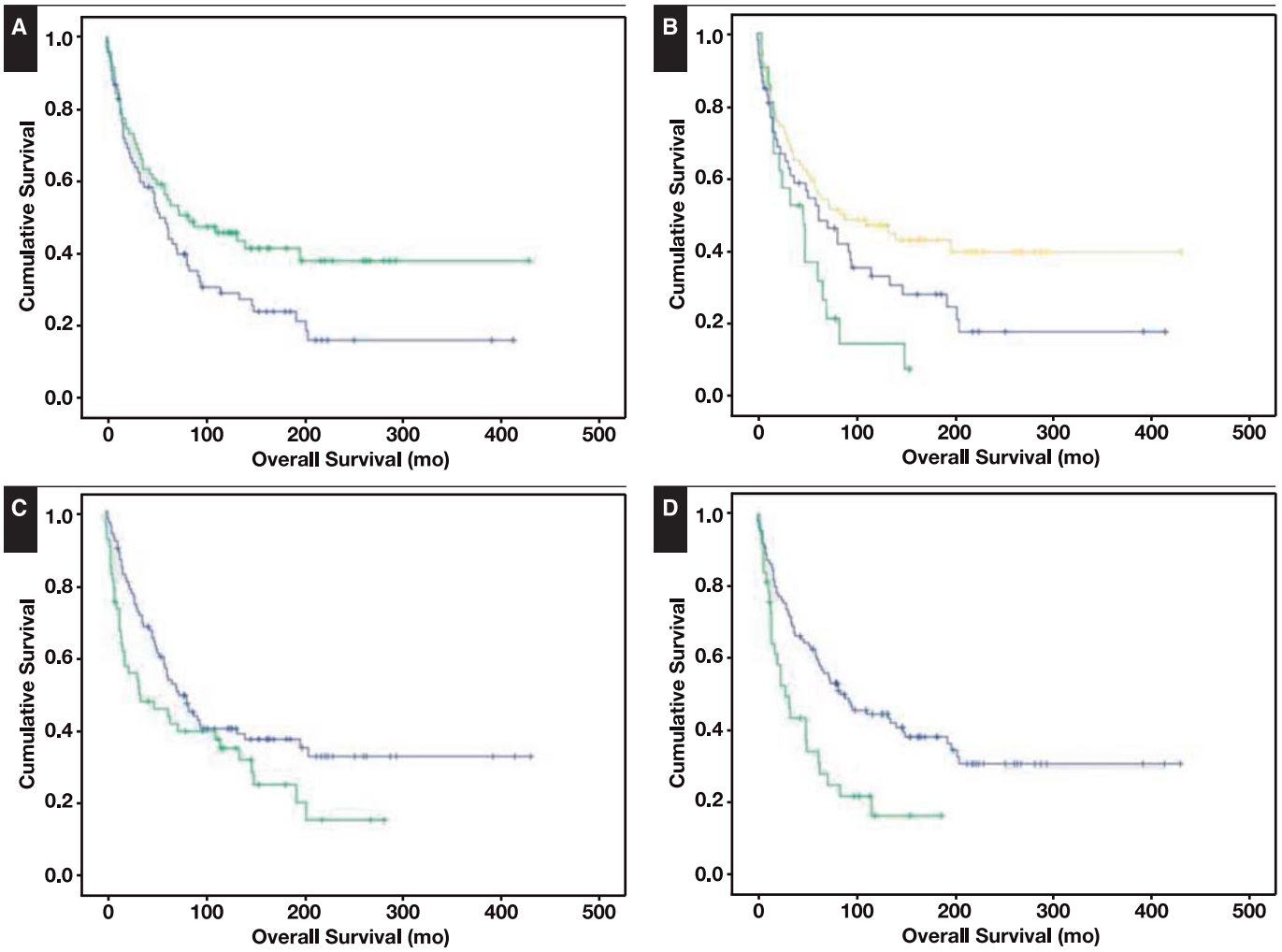


**Figure 2** Progesterone receptor (PR) expression score and staining intensity alone are significantly related to clinical outcome in stage I uterine leiomyosarcoma. **A**, PR score: Kaplan-Meier survival curve showing the association between PR expression score and overall survival (OS) for patients with stage I uterine leiomyosarcoma (n = 147; three patients with noninformative tumors). Patients with tumors that had PR score of 4 or more (n = 71, green line) had a median OS of 84 months (Cont.) vs 54 months for patients with tumors with a PR score of 3 or less (n = 76, blue line; $P = .042$). **B**, PR staining intensity: Kaplan-Meier survival curve showing the association between PR staining intensity and OS for patients with stage I uterine leiomyosarcoma (n = 147; three patients with noninformative tumors). Patients with tumors that had strong PR staining (n = 74, yellow line) had a median OS of 199 months vs 126 and 53 months for patients with tumors that stained negatively (n = 52, blue line) or weakly (n = 21, green line) for PR, respectively ($P = .014$). **C**, Age: Kaplan-Meier survival curve showing the association between patient age and OS for patients with stage I uterine leiomyosarcoma (n = 150). Patients 60 years or younger (n = 98, blue line) had a median OS of 74 months vs 34 months for patients older than 60 years (n = 52, green line; $P = .041$). **D**, Tumor diameter: Kaplan-Meier survival curve showing the association between the tumor diameter and OS for patients with stage I uterine leiomyosarcoma (n = 146; three patients with missing data). Patients with tumors measuring 10 cm or less (n = 109, blue line) had a median OS of 84 months vs 28 months for patients with tumors measuring more than 10 cm (n = 37, green line; $P = .001$).

stage I LMS, a finding that was retained in multivariate analysis. Similarly, strong PR staining intensity by itself, though not PR staining extent, was significantly related to longer survival in both univariate and multivariate analysis.

The clinical relevance of hormone receptors has been investigated in several studies.[7-14] Several of these analyzed small cohorts and may well have been underpowered, whereas others included carcinosarcomas, tumors that are currently believed to have a different histogenesis and biology. None of the previous studies assessed the role of hormone receptors as independent prognosticators in multivariate analysis.




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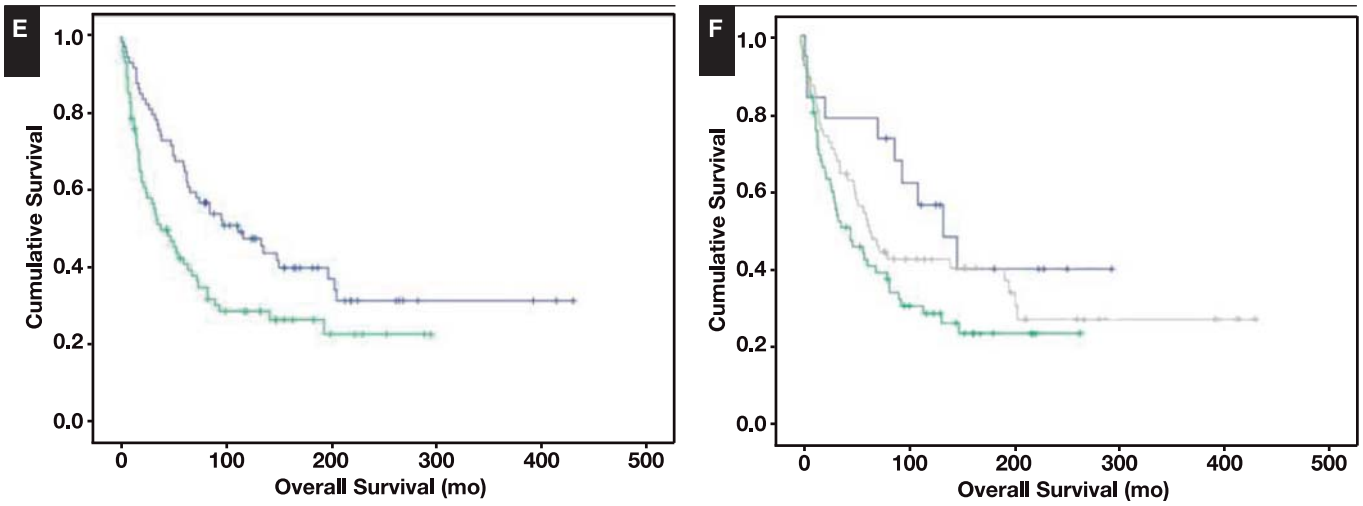


**Figure 2** (cont) **E**, Mitotic count: Kaplan-Meier survival curve showing the association between the mitotic count and OS for patients with stage I uterine leiomyosarcoma (n = 149; one patient with missing data). Patients with tumors that had 10 or fewer mitoses per 10 high-power fields (n = 74, blue line) had a median OS of 111 months vs 37 months for those with tumors having more than 10 mitoses per 10 high-power fields (n = 75, green line; $P = .007$). **F**, Atypia: Kaplan-Meier survival curve showing the trend for association between the degree of atypia and OS for patients with stage I uterine leiomyosarcoma (n = 148; two patients with missing data). Patients with tumors with mild atypia (n = 19, blue line) had a median OS of 135 months vs 47 and 65 months for those with tumors that had moderate (n = 66, green line) or severe (n = 63, gray line) atypia, respectively ($P = .087$).

**Table 4**
**Studies Assessing the Association Between Hormone Receptor Expression and Overall Survival in Uterine Leiomyosarcoma**

| Reference | Molecule | No. | Stage | Univariate *P* Value | Multivariate *P* Value | Prognosis |
|---|---|---|---|---|---|---|
| 7 | ER | 31 | All | .016 | NP | Good |
| 7 | PR | 31 | All | .016 | NP | Good |
| 8 | ER | 21 | All | NS | NP | — |
| 8 | PR | 21 | All | NS | NP | — |
| 9 | ER | 19 | All | .019 | NP | Good |
| 9 | PR | 19 | All | .023 | NP | Good |
| 10 | ER | 25 | All | NS | NP | — |
| 10 | PR | 25 | All | NS[a] | NP | — |
| 11 | ER | 43 | All | NS | NP | — |
| 11 | PR | 43 | All | .03[b] | NP | Good |
| Current | ER | 147 | I | NS | NS | — |
| Current | PR | 147 | I | .042 | .019 | Good |

ER, estrogen receptor; NP, not performed; NS, not significant; PR, progesterone receptor.
[a]Significant association with risk of recurrence.
[b]$P = .002$ for progression-free survival.

Data for previous studies in which cases of uterine LMS were analyzed as a separate entity, all consisting of less than 50 cases, and our current data are summarized in **Table 4**.[7-11]

In conclusion, we present what constitutes the largest study, to our knowledge, assessing the clinical role of hormone receptors in uterine sarcoma to date. In addition to the size of the cohort studied, it has the additional advantage of being a population-based analysis with a very long follow-up period (up to 430 months). Our data suggest that clinicopathologic parameters are far stronger prognosticators than ER or PR expression in analyses combining uterine sarcomas of all histologic types and/or stages. PR, but not ER, appears to have a prognostic role in stage I LMS.

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