Macrophage Inhibitory Cytokine 1: A New Prognostic Marker in Prostate Cancer

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Abstract

Purpose: High serum levels of macrophage inhibitory cytokine 1 (MIC-1) are strongly associated with metastatic prostate cancer, suggesting MIC-1 is a biomarker for prostate cancer prognosis.

Experimental Design: We conducted a prospective cohort study of 1,442 Swedish men with a pathologically verified diagnosis of prostate cancer between 2001 and 2003. Blood was drawn either pretreatment (n = 431) or posttreatment (n = 1,011) and cases were followed for a mean time of 4.9 years (range, 0.1-6.8 years).

Results: MIC-1 serum levels independently predicted poor cancer-specific survival with an almost 3-fold higher cancer death rate in patients with serum levels in the highest quartile compared with men with serum levels in the lowest quartile (adjusted hazard ratio, 2.98; 95% confidence interval, 1.82-4.68). Pretreatment MIC-1 levels revealed an even stronger association with disease outcome with an 8-fold higher death rate in the highest compared with the lowest category (adjusted hazard ratio, 7.98; 95% confidence interval, 1.73-36.86). Among patients considered to have localized disease, MIC-1 significantly increased the discriminative capacity between indolent and lethal prostate cancer compared with the established prognostic markers clinical stage, pathologic grade, and prostate-specific antigen level (P = 0.016). A sequence variant in the MIC-1 gene was associated with decreased MIC-1 serum levels (P = 0.002) and decreased prostate cancer mortality (P = 0.003), suggesting a causative role of MIC-1 in prostate cancer prognosis.

Conclusions: Serum MIC-1 concentration is a novel biomarker capable of predicting prostate cancer prognosis. (Clin Cancer Res 2009;15(21):6658–64)

Management of men with localized prostate cancer remains a major clinical challenge. The risk for overtreatment is substantial considering the excellent prognosis of a high proportion of men with untreated localized disease (1) and the morbidity associated with curative treatment (2). Currently, we lack adequate tools to safely discriminate between patients with prostate cancer that will follow a benign course and those with tumors that carry a poor prognosis and for whom curative therapy is indicated. Established prognostic factors for prostate cancer include clinical stage, pathologic grade, and serum prostate-specific antigen (PSA) concentrations (3–5). One biomarker that may improve the discriminatory capacity between lethal and nonlethal localized prostate cancer is macrophage inhibitory cytokine 1 (MIC-1).

MIC-1, a divergent member of the transforming growth factor-β superfamily, is commonly overexpressed in carcinomas including prostate cancer (6). MIC-1 serum levels predict disease relapse following radical prostatectomy (7) and improve the specificity of serum testing for prostate cancer (8). High serum levels of MIC-1 are strongly associated with presence of metastatic disease (6, 8) and a likely cause of cancer associated cachexia (9), suggesting that MIC-1 may be a valuable biomarker for prostate cancer prognosis.

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Serum MIC-1 Concentration and Prostate Cancer Prognosis

Translational Relevance

Prostate cancer is a leading cause of cancer death in Western countries. Because adverse effects are associated with therapy and most men affected with prostate cancer will die with—rather than from—prostate cancer, there is an urgent need for improved tools to distinguish lethal from indolent disease at diagnosis. In this study, we show for the first time the prognostic value of serum macrophage inhibitory cytokine 1 (MIC-1), a divergent member of the transforming growth factor-β superfamily, in prostate cancer. MIC-1 serum level was a significant predictor of prostate cancer death independently of established prognostic factors including clinical stage, pathologic grade, and prostate-specific antigen levels. Both pretreatment and posttreatment MIC-1 serum measurements provided prognostic information, and importantly, the strongest discriminative capacity was observed among patients considered to have organ-confined disease. Additional studies to validate MIC-1 as a prognostic marker in prostate cancer are warranted.

To assess the predictive value of MIC-1 in prostate cancer, we measured pretreatment and posttreatment MIC-1 serum concentrations in a large population-based cohort of incident prostate cancer patients with varying disease stage and related serum levels to prostate cancer–specific survival. Also, we assessed sequence variants in the MIC-1 gene with respect to MIC-1 serum levels and disease outcome.

Patients and Methods

Study cohort. Cancer Prostate in Sweden is a population-based case-control study of prostate cancer etiology with enrollment between January 2001 and October 2003. The study design has been described in detail elsewhere (10). Briefly, cases were all men between 35 and 79 y of age with pathologically verified adenocarcinoma of the prostate (ICD-10: C61). Clinical information such as clinical stage, pathologic grade, nodal or distant metastases, and diagnostic serum levels of PSA was obtained through linkage to the National Prostate Cancer Registry (Table 1; ref. 11).

Study participants donated blood 4.9 mo (range, 0.7-23.7 mo) on average, after date of diagnosis and serum was stored at -70°C until analysis. For the present study, serum samples from 1,442 prostate cancer cases were retrieved for measurement of serum levels of MIC-1 and PSA. Based on self-reported treatment, history samples were categorized as either pretreatment (n = 431) or posttreatment (n = 1,011). All participants gave written informed consent and the Research Ethics Committee at Karolinska Institutet and Umeå University approved this investigation.

Follow-up assessment. With the use of each study participant’s unique national registration number, vital status was assessed from date of blood draw up until January 15, 2008 through record linkage to the Swedish Population Registry. Prostate cancer–specific survival was obtained through linkage with the Cause of Death Registry up to December 31, 2005. Review of death certificates, done by an oncologist, established cause of death for individuals deceased after December 31, 2005.

Single-nucleotide polymorphism selection and genotyping. We defined a target genome region for the MIC-1 gene by including 15 kb of the promoter, all exons, introns, and 10 kb of the predicted 3’ untranslated region. Within this target region, haplotype tagging single-nucleotide polymorphisms (htSNP) were selected by applying aggressive tagging and a minimal coefficient of determination equal to 0.95 using Haploview version 4.1 (12). In total, 11 htSNPs were identified to capture the genetic variation within the selected target region. The htSNPs were genotyped in the complete study cohort using the MassARRAY system (SEQUENOM). Genotype consistency was 99.6% among control DNA with the average success rate among genotyped htSNPs was 96% (range, 92-99%). Each htSNP was in Hardy-Weinberg equilibrium among population control subjects.

Determination of MIC-1 and PSA serum levels. MIC-1 serum concentrations (pg/mL) were determined using a sensitive in-house sandwich ELISA, established using the mouse monoclonal antibody 26G6H6 for antigen capture and a sheep polyclonal antibody 23B3-P for detection, as previously described (13). All samples were assayed in triplicate and the coefficient of variation between samples was <12%. Total PSA was measured with the commercial version of a previously reported dual-label assay (DELFIA Prostat PSA F/T, PerkinElmer Life Sciences; ref. 14). The detection limit was 0.05 ng/mL with a coefficient of variation of 5.0% at 2.32 ng/mL and 13.9% at 0.34 ng/mL.

Statistical analysis. Unless otherwise noted, statistical analyses were done using R version 2.6.1 (15). Differences in MIC-1 serum levels between clinical characteristics were tested using the Kruskal-Wallis test. We performed time-to-event analysis using death from prostate cancer as outcome. Survival time was censored at time of death for patients dying from causes other than prostate cancer. Association between MIC-1 serum level and prostate cancer death was assessed in Cox regression analysis with serum levels categorized into four groups based on quartiles of the distribution of MIC-1 levels among all patients, with the lowest category used as reference group. Both crude analysis and analysis adjusted for the established prognostic markers (clinical stage, pathologic grade, nodal or distant metastases, serum PSA level, and age at blood draw) were done. In analysis stratified by prognostic risk group, we performed Cox regression analysis with logarithmically transformed MIC-1 levels included as a continuous variable. Proportionality was verified by visual inspection of the parallelism of the logarithms of the estimated cumulative hazards.

Multivariate logistic regression analysis was used to assess if MIC-1 serum levels, when used in combination with the established prognostic markers clinical stage, pathologic grade, nodal or distant metastases, serum PSA level, and age at blood draw, improved the discriminative capacity between indolent and fatal prostate cancer. Predicted probabilities of fatal cancer were applied to calculate receiver operating characteristic curves using the area under the curve (AUC) with 95% confidence interval (95% CI) as a measure of diagnostic performance. The assumption of linear association between the log odds and predictors was graphically assessed. The AUC of the model including both MIC-1 and established markers was compared with the AUC of the model including only the established markers using the method described by Hanley and coworkers (16), which accounts for the fact that the AUCs are derived from the same sample of patients, as implemented in STATA version 9.1 (17).

To acknowledge the presence of competing risks, we used the cmpsk Package for the R programming language, developed by Gray,9 to estimate cumulative incidence of prostate cancer mortality. We used Gray’s test (18) to assess differences in cumulative incidence between patients categorized according to quartiles of the distribution of MIC-1 levels.

All sequence variants were tested for deviation from Hardy-Weinberg equilibrium with the use of a permutation-based $\chi^2$ test. SNP genotypes were analyzed assuming an additive genetic model. Association between genotypes and MIC-1 serum levels was explored in linear regression analysis of logarithmically transformed MIC-1 serum levels, whereas association between genotypes and prostate cancer–specific survival was assessed in Cox regression analysis. All $P$ values reported were based on two-sided hypothesis.

**Results**

**MIC-1 serum levels and clinical characteristics.** Table 1 shows MIC-1 serum levels by clinical characteristics of patients. MIC-1 serum levels were significantly elevated across increasing level of clinical stage ($P < 0.0001$), nodal metastases ($P = 0.007$), distal metastases ($P < 0.0001$), Gleason score ($P < 0.0001$), and PSA level ($P < 0.0001$). Significantly higher MIC-1 levels were observed among patients receiving expectant or palliative treatment as compared to patients treated with curative intent ($P < 0.0001$).

**MIC-1 serum levels and prostate cancer death.** Overall, 380 (26%) of the 1,442 men died during follow-up, and of those, 265 (18%) had prostate cancer classified as their underlying cause of death. The mean follow-up time was 4.9 years (range, 0.1-6.8 years). After 6 years of follow-up, the cumulative incidence of death from prostate cancer was 7% and 34% among patients with MIC-1 serum concentrations below 710 and above 1,466 pg/mL, respectively ($P < 0.0001$; Fig. 1), corresponding to a 6-fold relative risk [hazard ratio (HR), 6.35; 95% CI, 4.13-9.77; Table 2]. In multivariate analysis that adjusted for the effects of the established prognostic factors clinical stage, pathologic grade, nodal or distant metastases, serum PSA level, and age at blood draw, higher MIC-1 levels...
remained associated with prostate cancer death (adjusted HR, 2.92; 95% CI, 1.82-4.68; Table 2).

We next performed separate assessment of MIC-1 serum levels among men with blood drawn pretreatment (n = 431) and posttreatment (n = 1,011). Compared with the total study cohort, we observed an even stronger association between pretreatment MIC-1 serum levels and prostate cancer survival (Table 2). Patients with the highest serum MIC-1 levels had a 12-fold higher death rate than those in the lowest category (HR, 12.08; 95% CI, 2.82-51.70). In adjusted analysis pretreatment, MIC-1 levels remained an independent prognostic factor with an 8-fold higher death rate in the highest compared with the lowest category (HR, 7.98; 95% CI, 1.73-36.86). Higher posttreatment MIC-1 serum levels were also associated with increased risk of prostate cancer death with an almost 6-fold higher death rate in the highest compared with the lowest category of MIC-1 serum levels (HR, 5.98; 95% CI, 1.42-3.92; Table 2). In analysis adjusted for established prognostic markers, posttreatment MIC-1 serum concentrations remained an independent predictor of prognosis (HR, 2.36; 95% CI, 1.42-3.92; Table 2).

**MIC-1 serum levels in patients with clinically localized disease.** We next restricted analysis to patients with clinically localized disease (T1/T2, N0/Nx, and M0/Mx). Cases were further stratified into low-risk (diagnostic PSA of <10 ng/mL and Gleason score of <7), intermediate-risk (diagnostic PSA of 10-20 ng/mL or Gleason score of 7), and high-risk (diagnostic PSA of >20 ng/mL and Gleason score of 8 and higher) categories. However, because only one patient died from prostate cancer during follow-up in the low-risk group, we pooled the low-risk and intermediate-risk groups. Cox regression analysis of logarithmically transformed MIC-1 serum levels revealed significant association with prostate cancer death both among men in the low/intermediate-risk group and among men in the high-risk group (P < 0.0001 and P = 0.0002, respectively; Table 3).

Analysis restricted to samples drawn pretreatment or posttreatment revealed significant association between MIC-1 and prostate cancer death both among men in the low/intermediate-risk

### Table 2. Risk of death from prostate cancer among 1,442 prostate cancer patients

<table>
<thead>
<tr>
<th>MIC-1 level (pg/mL)</th>
<th>No. of patients</th>
<th>No. of prostate cancer deaths</th>
<th>Crude HR (95% CI)</th>
<th>Adjusted HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All samples</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;710</td>
<td>362</td>
<td>25</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>710-1,006</td>
<td>359</td>
<td>51</td>
<td>2.11 (1.31-3.41)</td>
<td>1.39 (0.85-2.26)</td>
</tr>
<tr>
<td>1,006-1,456</td>
<td>360</td>
<td>68</td>
<td>2.91 (1.84-4.61)</td>
<td>1.61 (1.01-2.59)</td>
</tr>
<tr>
<td>&gt;1,456</td>
<td>361</td>
<td>121</td>
<td>6.35 (4.13-9.77)</td>
<td>2.92 (1.82-4.68)</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pretreatment samples</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;710</td>
<td>112</td>
<td>2</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>710-1,006</td>
<td>108</td>
<td>6</td>
<td>3.12 (0.63-15.47)</td>
<td>2.04 (0.39-10.57)</td>
</tr>
<tr>
<td>1,006-1,456</td>
<td>105</td>
<td>10</td>
<td>5.49 (1.20-25.04)</td>
<td>2.69 (0.54-13.41)</td>
</tr>
<tr>
<td>&gt;1,456</td>
<td>106</td>
<td>20</td>
<td>12.08 (2.82-51.70)</td>
<td>7.98 (1.73-36.86)</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Posttreatment samples</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;710</td>
<td>250</td>
<td>23</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>710-1,006</td>
<td>251</td>
<td>45</td>
<td>2.02 (1.22-3.34)</td>
<td>1.27 (0.76-2.12)</td>
</tr>
<tr>
<td>1,006-1,456</td>
<td>255</td>
<td>58</td>
<td>2.67 (1.65-4.33)</td>
<td>1.44 (0.87-2.38)</td>
</tr>
<tr>
<td>&gt;1,456</td>
<td>255</td>
<td>101</td>
<td>5.98 (3.80-9.42)</td>
<td>2.36 (1.42-3.92)</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*HRs from a multiple Cox model including serum MIC-1 levels, clinical stage, biopsy Gleason sum, serum PSA level, nodal and distal metastases, and age at blood draw as covariates.

### Table 3. Risk of death from prostate cancer among 872 patients with localized disease

<table>
<thead>
<tr>
<th>Risk group</th>
<th>No. of patients</th>
<th>No. of prostate cancer deaths</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All samples</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/intermediate</td>
<td>632</td>
<td>12</td>
<td>6.34 (2.46-16.29)</td>
<td>0.0001</td>
</tr>
<tr>
<td>High risk</td>
<td>240</td>
<td>31</td>
<td>3.31 (1.75-6.27)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Pretreatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/intermediate</td>
<td>256</td>
<td>6</td>
<td>7.00 (1.64-29.93)</td>
<td>0.009</td>
</tr>
<tr>
<td>High risk</td>
<td>79</td>
<td>7</td>
<td>4.26 (1.29-14.09)</td>
<td>0.018</td>
</tr>
<tr>
<td>Posttreatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/intermediate</td>
<td>376</td>
<td>6</td>
<td>5.84 (1.64-20.80)</td>
<td>0.006</td>
</tr>
<tr>
<td>High risk</td>
<td>161</td>
<td>24</td>
<td>3.06 (1.42-6.57)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*NOTE: The prognostic role of MIC-1 serum level is tested within each prognostic risk group category. Logarithmically transformed MIC-1 serum level was modeled as a continuous variable.
Importantly, in patients considered to have localized disease, material effect on the independent prognostic value of MIC-1. Clinically significant associations were found with established prognostic factors, including clinical stage, pathologic grade, and serum PSA levels. In multivariate analysis, adjustment for the established prognostic factors increased the discriminative capacity of MIC-1 levels compared with established markers. In analysis restricted to patients with clinically localized disease, no significant improvement in discriminative capacity was observed by inclusion of MIC-1 serum levels (Table 4).

**Genotype, haplotype, MIC-1 serum levels, and prostate cancer death.** Individual tests of each SNP revealed nominally significant associations between log-transformed MIC-1 serum levels and four sequence variants: rs1363120, rs888663, rs1227732, and rs1054564. All these four variants reached a Bonferroni-adjusted P value of 0.004 that is required for a 5% study-wide significance level in 11 independent tests (Table 5). For variants rs1363120, rs888663, and rs1227732, we observed decreasing levels of MIC-1 across increasing number of rare alleles carried, whereas for the sequence variant rs1054564, we observed increasing MIC-1 levels across increasing number of rare alleles carried.

Only one sequence variant showed study-wide significant association with risk of prostate cancer death (rs1227732, \( P = 0.003 \); Table 5). Of note, the rare allele of rs1227732 was associated with decreased risk of prostate cancer death as well as decreasing levels of serum MIC-1 concentrations.

**Discussion**

This study shows the prognostic value of serum MIC-1 levels in the prediction of prostate cancer death. In multivariate analysis, adjustment for the established prognostic factors (i.e., clinical stage, pathologic grade, and serum PSA levels) did not materially affect the independent prognostic value of MIC-1. Importantly, in patients considered to have localized disease, an elevated serum MIC-1 level was an independent predictor of prostate cancer death.

Due to the increasing use of PSA screening, an increasing proportion of men diagnosed with prostate cancer have a very low risk of prostate cancer death. Because progression-free survival in patients with localized disease managed with watchful waiting is high (1, 19) and disease outcome cannot be accurately predicted, overtreatment of patients with low-risk disease is common. Management by active surveillance with selective delayed intervention based on early PSA changes has been proposed as a strategy to reduce overtreatment of patients with indolent disease (20). However, although both baseline PSA measurements and rate of PSA change may be important prognostic factors, they poorly distinguish those who will develop a lethal prostate cancer (21). We show that both pretreatment and posttreatment serum MIC-1 levels improve the prediction of outcome in patients with organ-confined disease. Therefore, high-serum levels of MIC-1 at diagnosis may be used to improve the identification of patients that might benefit from early systemic adjuvant treatment in addition to local treatment.

Our finding that increased serum MIC-1 concentrations are strongly associated with advanced disease and progression of prostate cancer is consistent with previous studies (6, 8, 22-24). Welsh and coworkers (6) reported that patients with metastatic prostate cancer markedly overexpressed MIC-1 protein within tumors, and that this resulted in increased serum concentrations of MIC-1. Tumor stromal–associated MIC-1 has been linked to prostate cancer outcome following radical prostatectomy, with decreasing stromal levels associated with increasing circulating MIC-1 levels and independent prediction of disease relapse (7). Selander and coworkers (25) recently showed significantly higher serum MIC-1 levels in patients with baseline bone metastases when compared with patients without bone metastases. In addition, patients who experienced bone relapse during a mean follow-up of 3 years had significantly higher baseline levels of MIC-1 compared with patients who did not experience bone relapse during follow-up, suggesting that MIC-1 provides prognostic information about future tumor behavior.

Despite the strong relationship of MIC-1 to cancer, its role in tumorigenesis is not well understood (reviewed in ref. 26). The

### Table 4. Areas under receiver operating curves for logistic regression models predicting death from prostate cancer

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All samples</td>
</tr>
<tr>
<td>All patients</td>
<td>0.87 (0.85-0.89)</td>
</tr>
<tr>
<td>Established risk factors*</td>
<td>0.88 (0.86-0.90)</td>
</tr>
<tr>
<td>( P )</td>
<td>0.016</td>
</tr>
<tr>
<td>Patients with localized disease</td>
<td></td>
</tr>
<tr>
<td>Established risk factors*</td>
<td>0.82 (0.76-0.89)</td>
</tr>
<tr>
<td>Established risk factors plus MIC-1</td>
<td>0.83 (0.77-0.90)</td>
</tr>
<tr>
<td>( P )</td>
<td>0.27</td>
</tr>
</tbody>
</table>

*Established risk factors included clinical stage (continuous variable), pathologic grade (continuous variable), nodal metastases (yes or no), distant metastases (yes or no), attained age (continuous variable), and serum PSA level (continuous logarithmically transformed variable). Nodal and distant metastases were not included as risk factors in the analysis of patients with clinically localized disease. Serum level of MIC-1 was logarithmically transformed and modeled as a continuous variable.

\footnote{\( P \) values are for the comparison between the model with established risk factors and the model with established risk factors plus MIC-1.}
majority of studies report an antitumorigenic role of MIC-1 in regulating tumor growth (27–29) through induction of apoptosis (30); however, enhancement of tumorigenic activity has also been reported (31). We observed significant association between common genetic variation in the MIC-1 gene and both MIC-1 serum levels and prostate cancer–specific survival, suggesting a functional role of MIC-1 in prostate cancer progression. Intriguingly, all associated variants are located in noncoding regions. The variant rs1227732, associated with decreased MIC-1 serum levels as well as decreased risk of prostate cancer death, is located in the intronic region of MIC-1 (MIC-1 has only two exons and one intron). Further studies are warranted to explore possible functional properties, such as gene transcription alteration, of this variant.

Strengths of our study include its large size, prospective design, complete follow-up, and valid end point; prostate cancer death has been shown to be accurately registered in the Swedish Cause of Death Register (32). A limitation of this study is the low proportion of prostate cancer deaths observed in patients with low-risk disease. Although MIC-1 serum levels were independently associated with increased risk of prostate cancer death, the AUC was not significantly increased among patients with localized disease, a patient group for which improved risk assessment is most crucial. This may reflect lack of statistical power due to small number of events and additional studies exploring the predictive value of MIC-1 among patients with localized disease is warranted.

In conclusion, with the use of serum MIC-1 concentrations, we were able to stratify prostate cancer patients into groups with substantially different prostate cancer mortality. There was an association between both pretreatment and posttreatment serum MIC-1 levels and clinical outcome in patients with clinically localized disease, a group whose prognosis is difficult to assess. Further prospective studies to validate MIC-1 as a prognostic marker in prostate cancer and to construct an optimal predictive model of lethal prostate cancer are warranted.

Disclosure of Potential Conflicts of Interest

D. Brown and S. Breit are named inventors on patents held by St. Vincent’s Hospital. The other authors disclosed no potential conflicts of interest.

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References


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