A Meta-analysis of Reverse Transcriptase–Polymerase Chain Reaction for Tyrosinase mRNA as a Marker for Circulating Tumor Cells in Cutaneous Melanoma

Hensin Tsao, MD, PhD; Uma Nadiminti, BA; Arthur J. Sober, MD; Michael Bigby, MD

**Objective:** To systematically review the use of reverse transcriptase–polymerase chain reaction (RT-PCR) for tyrosinase messenger RNA as a molecular serum marker for metastatic melanoma.

**Data Sources:** Computerized searches (1966-1999) of the PubMed and MDConsult databases and a manual search of retrieved article references.

**Study Selection:** Cohort studies containing test subjects and negative controls were reviewed.

**Data Extraction:** Three investigators independently screened abstracts for relevant studies and 2 investigators independently reviewed all eligible studies.

**Data Synthesis:** Of 127 identified studies, 50 were reviewed in detail and 23 met all inclusion criteria. From these 23 studies, the PCR methods, the total number of patients, the number of control subjects, and the number of RT-PCR–positive patients per stage were analyzed. Results of RT-PCR for tyrosinase messenger RNA were positive in 18% (95% confidence interval [CI], 3%-22%) patients for stage I disease, 28% (95% CI, 23%-34%) for stage II disease, 19% (95% CI, 16%-21%) for stage I/II localized disease, 30% (95% CI, 26%-34%) for stage III disease, and 45% (95% CI, 41%-50%) for stage IV disease. Specificities were 100% in all but 1 study. Results of RT-PCR were positive in only 0.4% of healthy controls and patients with nonmelanoma cancer.

**Conclusions:** The lack of data on the outcome of stage I, II, and III patients who were RT-PCR positive and the low prevalence of RT-PCR positivity in patients with known stage IV disease limit the applicability of this test at this time. Ongoing and future studies on a quantitative RT-PCR, amplification of multiple melanoma-associated antigens, and use of the test as a prognostic indicator might improve the utility of this molecular serologic tool.

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Efforts to favorably impact cancer mortality have led to a rising interest in serologic markers, such as prostate-specific antigen. In theory, a valuable tumor marker should be able to clarify diagnosis, quantitatively measure therapeutic response, and more accurately predict outcome. Although prostate-specific antigen is one of the most frequently used serum tumor markers, the utility of this test as a screening and surveillance tool still remains controversial.

Cutaneous melanoma has grown rapidly in incidence during the past several decades. In 2000, an estimated 47,700 cases of cutaneous melanoma occurred, with 7,700 deaths in the United States. Although the prognosis of cutaneous melanoma best correlates with tumor thickness, there has been much interest in recent years on more sensitive and specific serologic markers for advanced disease. Radiolabeled monoclonal antibodies against melanoma antigens have been used to target and image metastatic deposits, al-
MATERIALS AND METHODS

We used MDConsult and PubMed (which includes MEDLINE, PreMEDLINE, and HealthSTAR) to conduct a computerized search for articles containing “PCR,” “tyrosinase” and “melanoma” as text keywords (not Medical Subject Headings). We included articles indexed between January 1, 1986, and December 31, 1999. Three of us (H.T., A.J.S., and U.N.) initially screened the titles and abstracts for relevance; articles that were considered pertinent were retrieved and reviewed in full. Relevance was defined as original published clinical investigations (excluding ill-defined abstracts from proceedings of meetings) pertaining to patients with melanoma (not animal models or in vitro cell line studies) involving peripheral blood molecular analysis. The bibliographies of all reviewed articles were then further cross-referenced for unaccounted studies.

The following criteria were used to select articles to include in this review:

1. Primary cohort studies of patients with melanoma and not review articles, abstracts, or preliminary reports.
2. Studies with clearly identified negative (“no disease”) controls (healthy individuals or patients with cancer but not melanoma).
3. The stage of the melanoma is clearly stated at the time of RT-PCR analysis. In some studies, a 3-stage system was used: stage I, localized disease; stage II, regional nodal metastases; and stage III, distant metastases. In other studies, a 4-stage system was used: stage I, localized melanoma 1.5-mm or less thick; stage II, localized melanoma greater than 1.5-mm thick; stage III, regional nodal metastasis; and stage IV, distant metastasis.
4. Studies that examined cutaneous melanoma (uveal and other melanomas were excluded).
5. Studies that examined tyrosinase as a distinct reported molecular marker. Studies that examined other markers but did not separate tyrosinase from the analysis were excluded.
6. Studies that included analysis of peripheral blood samples. Studies limited to nodal RT-PCR were excluded.
7. Studies in which the RT-PCR status of individuals, not specimens, were clearly defined. In studies in which multiple samples were obtained from an individual, the status of the patient was considered not the status of the blood specimens. Studies that do not report patient status but only specimen positivity were excluded; in these studies, multiple positive samples from a positive individual may skew the analysis.
8. Studies with no overlapping populations (inclusion of duplicate articles written on a single group of patients would falsely elevate the total number of patients and inappropriately emphasize the results of the study).

After these criteria were imposed, we found approximately 50 publications addressing the utility of tyrosinase RT-PCR as a serologic and nodal staging tool. Smith et al9 first devised an assay to detect tyrosinase messenger RNA (mRNA) in the peripheral blood of patients with metastatic melanoma. Since this initial publication, there has been waxing enthusiasm for this assay in the scientific and lay communities. To date, there have been approximately 50 publications addressing the utility of tyrosinase RT-PCR as a serologic and nodal staging tool (RT-PCR) as a highly sensitive molecular diagnostic tool, Smith et al9 first devised an assay to detect tyrosinase messenger RNA (mRNA) in the peripheral blood of patients with metastatic melanoma. Since this initial publication, there has been waxing enthusiasm for this assay in the scientific and lay communities. To date, there have been approximately 50 publications addressing the utility of tyrosinase RT-PCR as a serologic and nodal staging tool.

DATA EXTRACTION

Each article was then analyzed independently by 2 of us (H.T. and U.N.) in detail, and pertinent results were obtained from each study. For each article, we assessed whether (1) an independent, masked comparison with a reference standard was used; (2) the spectrum of patients was appropriate for the clinical setting; (3) the details of the PCR reaction were sufficiently detailed; and (4) the results affected the decision to perform standards.

For each study, multiple 2 × 2 tables were constructed for patients based on 3-stage and 4-stage systems. For studies that used the American Joint Committee on Cancer (AJCC) 4-stage system, we examined stages I, II, I/II (localized disease), III, and IV in separate 2 × 2 analyses. For studies that used a 3-stage system, we considered stage I as localized disease (combined with stage I/II aggregate in the AJCC 4-stage system), stage II as regional disease (combined with stage III in the AJCC 4-stage system), and stage III as distant disease (combined with stage IV in the AJCC 4-stage system). Thus, in the final construction, the AJCC 4-stage system was used and the 3-stage system was converted to the current 4-stage nomenclature. Five 2 × 2 tables were created for stages I, II, I/II, III, and IV.

There was no quantitative cutoff level for an RT-PCR-positive result. A result was considered positive if a band, which corresponded to the predicted amplicon size, was visualized on an ethidium bromide–stained agarose gel.

For each study, we determined whether an independent, masked-comparison standard diagnostic test of disease was applied, whether RT-PCR was evaluated in an appropriate spectrum of patients, and whether the criterion standard was applied regardless of the results of RT-PCR.

ANALYSIS

Meta-analysis was performed using the META-ANALYST software program (Joseph Lau, New England Medical Center, Boston, Mass). Raw data from all the studies were pooled, and overall sensitivity and specificity were determined for patients in stages I, II, I/II (localized disease), III, and IV. For each aggregate stage analysis, the number of negative control patients was the sum of the negative controls used in each study that contributed to the pooled test population in that stage. Pooled likelihood ratios were calculated using META-ANALYST’s random effects model. The likelihood of a positive test result (LR+) is defined as the percentage of people with disease who have a positive result divided by the percentage of people without disease who have a positive result. The likelihood of a negative test result (LR−) is defined as the percentage of people with disease who have a negative result divided by the percentage of people without disease who have a negative result. Traditionally, LR+=sensitivity/(1–specificity) and LR−=(1−sensitivity)/specificity.
tool. Because a critical body of literature now exists evaluating tyrosinase mRNA in the peripheral blood of patients with cutaneous melanoma, we performed a meta-analysis of the extant studies to determine the specificity, sensitivity, and likelihood ratio of this RT-PCR assay and attempted to assess its usefulness and limitations in clinical practice.

RESULTS

The PubMed and MDConsult searches yielded 127 and 90 titles, respectively; all relevant articles from the MDConsult search were contained in the PubMed search results. Of these, 50 studies were reviewed in detail and 23 met all inclusion criteria.10-32

The spectrum of patients was biased for advanced disease. For instance, several studies11,16,22,28,31 included only stage III or IV patients. Of the 23 studies, only 712-14,18,21,27,29 specifically delineated their methods for staging patients with melanoma. Most studies relied on the history, physical examination, chest radiograph, and complete blood cell count for their staging procedure. Nine studies13,14,16,18,21,24,27,28,30 also provided information regarding the timing of blood sample collection relative to staging or therapeutic procedures. Patients were multiply sampled in 9 studies12,15,19,21,26,27,29-31; however, negative controls in these studies were never sampled over time.

The aggregate number of RT-PCR tyrosinase-positive patients and the total number of tested patients are shown in Table 1. Of 1799 patients analyzed in 23 studies, RT-PCR was positive for tyrosinase in 52 of 291 in stage I, 84 of 296 in stage II, 151 of 806 with localized disease (stage I/II in the 4-stage system+stage I in the 3-stage system), 146 of 492 in stage III, and 227 of 501 in stage IV. Since the stage I (n=291) and stage II (n=296) were included in the stage I/II localized disease population (n=806), these duplicates were not counted in the final total (N=1799).

<table>
<thead>
<tr>
<th>Study</th>
<th>Total Analyzed</th>
<th>Stage I (Localized)</th>
<th>Stage II (Localized)</th>
<th>Stage I/II (Localized)</th>
<th>Stage III (Regional)</th>
<th>Stage IV (Distant)</th>
<th>Negative Controls</th>
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<td>64</td>
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<td>2/28</td>
<td>11/24</td>
<td>9/12</td>
<td>0/15</td>
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<td>102</td>
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<td>NS</td>
<td>NS</td>
<td>1/43</td>
<td>0/15</td>
<td>12/44</td>
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<td>Smith et al,21 1991</td>
<td>7</td>
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<td>26/67</td>
<td>53/154</td>
<td>24/49</td>
<td>24/32</td>
<td>0/41</td>
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<td>NS</td>
<td>NS</td>
<td>6/46</td>
<td>7/41</td>
<td>16/36</td>
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<td>66</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>8/18</td>
<td>16/32</td>
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<td>65</td>
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<td>NS</td>
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<td>73</td>
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<td>NS</td>
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<td>0/4</td>
<td>1/6</td>
<td>1/10</td>
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<td>29/29</td>
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<td>Schittke et al,28 1999</td>
<td>225</td>
<td>13/74</td>
<td>8/45</td>
<td>21/119</td>
<td>8/48</td>
<td>21/58</td>
<td>0/40</td>
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<td>Curry et al,29 1999</td>
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<td>4/13</td>
<td>30/76</td>
<td>34/97</td>
<td>55/97</td>
<td>0</td>
<td>0/50</td>
</tr>
<tr>
<td>Hanekom et al,30 1999</td>
<td>165</td>
<td>4/76</td>
<td>6/67</td>
<td>10/143</td>
<td>0/10</td>
<td>0/12</td>
<td>0/1</td>
</tr>
<tr>
<td>Alao et al,31 1999</td>
<td>21</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1/4</td>
<td>5/17</td>
<td>0/12</td>
</tr>
<tr>
<td>Tessier et al,32 1997</td>
<td>85</td>
<td>0</td>
<td>0</td>
<td>0/42</td>
<td>0/20†</td>
<td>16/23</td>
<td>0/20</td>
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<td>Kopreski et al,33 1999</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0/4</td>
<td>4/6</td>
<td>0/20</td>
</tr>
<tr>
<td>Total</td>
<td>1799</td>
<td>52/291</td>
<td>84/296</td>
<td>151/806</td>
<td>146/492</td>
<td>227/501</td>
<td>2/521</td>
</tr>
</tbody>
</table>

*Data are given as number of tyrosinase-positive patients/total number of patients in the particular stage. NS indicates not separated.
†Thirty-two high-risk post-nodal dissection patients were not included (58 samples, not patients, tested).
‡Negative at initial testing with other specimens. Patients were retested with transient positivity.

Table 2. Overall Sensitivity, Specificity, and Likelihood Ratios According to Stage of Disease*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Sensitivity (95% CI), %</th>
<th>Specificity (95% CI), %</th>
<th>Likelihood Ratio + (95% CI)†</th>
<th>Likelihood Ratio − (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>18 (3-22)</td>
<td>100 (99-100)</td>
<td>7 (2-28)</td>
<td>0.8 (0.7-0.9)</td>
</tr>
<tr>
<td>II</td>
<td>28 (23-34)</td>
<td>100 (99-100)</td>
<td>13 (4-41)</td>
<td>0.7 (0.6-0.8)</td>
</tr>
<tr>
<td>I/II (localized)</td>
<td>30 (26-34)</td>
<td>100 (99-100)</td>
<td>8 (4-15)</td>
<td>0.8 (0.7-0.9)</td>
</tr>
<tr>
<td>III</td>
<td>45 (41-50)</td>
<td>100 (99-100)</td>
<td>12 (6-22)</td>
<td>0.6 (0.5-0.7)</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval.
†The likelihood of a positive test result. See the “Analysis” subsection of the “Materials and Methods” section for a definition.
‡The likelihood of a negative test result. See the “Analysis” subsection of the “Materials and Methods” section for a definition.
Thus, RT-PCR was positive for tyrosinase mRNA in 18% (95% confidence interval [CI], 3%-22%) of patients with stage I disease, 28% (95% CI, 23%-34%) with stage II disease, 19% (95% CI, 16%-21%) with stage III localized disease, 30% (95% CI, 26%-34%) with stage III disease, and 45% (95% CI, 41%-50%) with stage IV disease (Table 2). Two of 521 negative control persons had positive RT-PCR reactions. These controls included healthy individuals and patients with cancers other than melanoma (“cancer controls”). The extremely low false-positive rate among the control population (2/521 or 0.38%) yields uniformly high specificity (Table 2). The sensitivity for each stage is calculated based on the total number of negative control cases generated from the stage-appropriate studies.

The LR+ for each stage is underestimated because most studies had no false-positive results. By design, META-ANALYST adds 0.5 to all the zeros in calculating the LR+. The LR− is close to 1 for all stages. Thus, a negative test result will not significantly change the probability of disease.

For most studies, blood samples for RT-PCR were obtained at the time of staging. Some studies used radiologic examinations and blood tests to determine the stage of disease, whereas most studies did not specify tests beyond clinical examination. There was no independent, masked-comparison standard diagnostic test of disease described or applied in the studies. For most studies, the method of patient selection was not described in detail.

There has been growing enthusiasm for molecular serologic markers to aid in the diagnosis and prognosis of patients with melanoma; however, to date, the results have been variable. Tyrosinase is an attractive candidate marker because expression of this gene is relatively limited in distribution.9 Our meta-analysis suggests, however, that RT-PCR for tyrosinase mRNA in the blood of patients with melanoma is of limited value given the unreliability of the test at the current time. Although there is a general trend toward increasing prevalence with greater tumor volume (18% for stage I and 45% for stage IV disease), the failure of the current test to identify more than half of the patients with known metastatic disease restricts its use in the clinical setting.

There are several procedural and methodological problems in reviewed studies that further limit the usefulness of RT-PCR. There was a bias in enrollment in many of the studies. The distribution of localized, regional, and distant disease is clearly skewed toward advanced disease compared with the population-based incidence.31 Investigators might have recruited patients with known metastatic disease to optimize the prevalence of a positive RT-PCR result. Alternatively, because many studies originated from oncology units, patients with early disease might have been excluded purely by referral bias or included because the patients have high risk for future recurrence. Consecutive enrollment in a multidisciplinary unit or random selection of patients would lead to a more accurate disease distribution.

Many studies collected multiple samples and performed multiple analyses on the same patient population. Follow-up analyses were usually obtained during routine interval surveillance. However, the negative control populations were not sampled at the same frequency. Thus, there is selective multiple sampling of a high-risk population, with minimal sampling of healthy individuals. This practice can potentially increase the false-positive rate in high-risk patients and decrease the false-positive rate in healthy donors, thus leading to an apparent improvement in sensitivity and specificity. If multiple sampling is to be used, nondiseased controls, patients with early disease, and patients with late disease should be sampled at equivalent intervals. Several groups12,21,30 sampled patients’ blood over time during follow-up, and results from these small series suggest that positive tyrosinase detection might be negatively associated with disease-free survival.

In addition to blood sample collection, sample processing might also increase variability. Three sources of RNA have been used in various studies: whole blood, plasma-depleted whole blood, and density-gradient-purified mononuclear cells. Because whole blood and plasma-depleted whole blood contain abundant erythrocyte RNA, the amount of tyrosinase mRNA is diminished relative to total RNA. On the other hand, density-gradient-purified mononuclear cells, in theory, enrich tyrosinase mRNA by eliminating erythrocyte RNA contamination; however, the additional processing might also lead to loss of cells or RNA degradation. In a series of 50 stage IV patients, Jung et al16 found that 10% of patients were RT-PCR positive with whole blood preparations and 26% were positive after Ficoll-Hypaque density gradient purification. One patient, however, who was positive by whole blood amplification became negative after density gradient purification. Delays in sample processing and improper mRNA extraction protocols can lead to technical false negatives and underestimate the sensitivity of the RT-PCR procedure. More uniform sampling of individuals and processing of blood need to be adopted in future methods.

Most studies used 2 rounds of PCR (30 cycles each) with nested primers, as defined by Smith et al.10 In the original study, a second round of amplification enhanced detection. In spiking experiments, several investigators17,32,34 documented the sensitivity of RT-PCR tyrosinase to be in the range of 1 melanoma cell in 1 to 10 mL of blood, depending on the melanoma cell line used as positive controls. Because the body contains approximately 5 L of blood,35 the approximate number of steady state circulating melanoma cells required for detection is 1000 (5000 mL/L cell per 5 mL). Because this steady-state pool of blood-borne melanoma cells is a function of tumor shedding and tumor clearance, inconsistent shedding can lead to variable results. To this end, Reinhold et al19 observed that in 8 hours, 2 patients oscillated between being RT-PCR positive and negative, suggesting that tumor cell shedding might be intermittent and unpredictable. This oscillation suggests low volume release or infrequent shedding. To remain above the detection threshold consistently, the tumor can shed large amounts of cells at infrequent intervals (eg, once-a-day intravenous drug delivery model) or small amounts of cells at frequent intervals (eg, tetanus model). In both models, the rate of tumor release into the blood must initially exceed the rate of tumor clearance from the...
blood, otherwise a detectable pool of circulating tumor cells would never be established.

Given the sensitivity of the nested PCR technique itself, it is somewhat surprising that there were so few false positives in the healthy donor and nonmelanoma cancer population. Hanekom et al reported 1 false-positive tyrosinase RT-PCR reaction in 50 healthy controls and concluded that the frequency of melanocyte contamination from needlesticks was 2%. Evidence from the literature suggests that the contamination rate is almost 10-fold less (0.37%).

The uniformly high specificity results from the low false-positive rate. However, the low false-positive rate might be artifactual as a result of study design. In almost all studies, healthy donors and patients with nonmelanoma cancer are considered the “no disease” cohort. If this is the case, then all patients with melanoma, regardless of bloodborne disease, would be considered the “disease” cohort. The test is then designed for diagnosis. Alternatively, if RT-PCR is aimed at early detection of hematogenous disease and prognostication, then metastatic melanoma should be considered the disease cohort and localized cutaneous melanoma should compose the no disease cohort. This construct, however, is also inaccurate because a certain percentage of patients with localized disease will experience recurrence with time, and thus these patients can be expected to harbor circulating melanoma cells. Because the gold standard for no disease is difficult to define, most investigators performed analyses with prognosis in mind but diagnosis in design. The true “hematogenous disease” group would be a cohort of patients with localized disease who survive 5 or 10 years without evidence of recurrence. However, in most of the published studies, staging was performed around the time the blood sample was drawn. Furthermore, Tessier et al reported that transient release of melanocytes into the bloodstream can occur after surgery. Thus, other negative controls to be considered in future studies include surgical patients without melanoma (eg, patients undergoing Mohs surgery), patients with atypical moles without melanoma, and post–UV-irradiated patients.

Except in one study, there were no positive RT-PCR reactions in the control population. The LR+ is thus calculable for most stages because the denominator is zero. META-ANALYST handles this problem by adding 0.5 to the control group as a mathematical correction. Because many studies have a small control population (some with fewer than 10 individuals), the correction itself distorts the calculation and invalidates the utility of the LR+ in clinical decision making. On the other hand, the LR+ is calculable but ranges from 0.6 (stage IV) to 0.9 (localized disease). The proximity of these values to unity argues that a negative test result will not significantly change the probability of disease. As the test stands now, neither a positive nor a negative result will confidently alter the probability of having disease or having no disease, respectively. However, the low false-positive rate suggests that an individual with a positive RT-PCR result is unlikely to be healthy.

One area for future investigation is the expansion of prognostic studies based on RT-PCR status. Several groups have observed significantly reduced disease-free survival and overall survival for patients with melanoma who are RT-PCR positive; however, others have not found this correlation. Battayani et al found a greater likelihood of progression (ie, doubling of tumor volume) within 4 months in patients with a positive RT-PCR result. These early results suggest that RT-PCR for tyrosinase might be useful in the future as a prognostic indicator. However, at the current time, the inconsistencies preclude useful applications.

Because the sensitivity of the test seems variable between research sites, a large multicenter trial with a uniform collection protocol and a central reference laboratory is desirable. Furthermore, preliminary attempts at quantitative measurements should be further developed to generate a prostate-specific antigen–like serum tumor marker. Finally, use of multiple melanoma antigens as RT-PCR markers might enhance sensitivity and specificity.

In conclusion, RT-PCR for tyrosinase and other melanoma-associated antigens offers promise as a widely applicable molecular tumor marker. However, low sensitivity and interlaboratory variability limits its clinical utility at the current time. Moreover, the usefulness and cost-effectiveness of RT-PCR relative to other emerging serologic markers for melanoma, such as circulating S100 protein, remains to be established.

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REFERENCES


